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CONTENTS OF VOLUME XXXIV

NUMBER 1, JANUARY-FEBRUARY, 1967

	PAGE
OBITUARY: HENRY HORN, M.D.....	1
MORTALITY AMONG YOUNG NARCOTIC ADDICTS. <i>Percy Mason, M.D.</i>	4
SPONTANEOUS DISAPPEARANCE OF PULMONARY METASTASES IN HYPER- NEPHROMA: FINAL REPORT OF TWENTY YEAR FOLLOW-UP AFTER NEPHRECTOMY. <i>Hans E. Shapira, M.D., and Gordon D. Oppenheimer, M.D.</i>	11
CLINICAL EVALUATION OF PATIENTS WITH NEUROMUSCULAR DISORDERS. <i>Paul Slotwiner, M.D.</i>	17
OBSERVATIONS ON SOME METHODS OF CLINICAL NEUROPHYSIOLOGY. <i>Sidney P. Diamond M.D.</i>	25
HERNIATION AND STRANGULATED INCARCERATION OF SMALL INTESTINES IN THE FORAMEN OF MORGAGNI. <i>Giuseppi Rossi, M.D., and Marshall Weiss, M.D.</i>	38
UNUSUAL PROBLEMS IN SURGERY. <i>Lewis Burrows, M.D., and Jack Rudick, M.D., Editors</i>	
PRIMARY MESENTERIC VENOUS THROMBOSIS.....	40
LYMPHANGIOMA OF THE RETROPERITONEUM AND MESENTERY.....	47
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Ktton, M.D., Editor</i>	
HYPERCALCEMIA AND AZOTEMIA WITH TERMINAL HYPOTENSION....	52
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Editors</i>	
RETICULUM CELL SARCOMA INVOLVING STOMACH AND SMALL BOWEL....	60
RETICULUM CELL SARCOMA INVOLVING LYMPH NODES OF SMALL BOWEL MESENTERY.....	61
MELANOSARCOMA WITH GASTRIC AND SMALL BOWEL METASTASES.....	66
CALCIFYING HEPATIC METASTASES FROM COLONIC ADENOCARCINOMA....	68
COMPUTER ANALYSIS OF THE ELECTROCARDIOGRAM. <i>Leon Pordy, M.D., Harry Jaffe, M.D., Kenneth Chesky, M.D., Charles K. Friedberg, M.D., Raymond E. Bonner, D.Eng., Herbert D. Schwetman, M.A., and David Alexander, B.S.E.E.</i>	71
ANNOUNCEMENT: RALPH COLP AWARD WINNER. <i>Irwin M. Gelernt, M.D., and Sigmund H. Ein, M.D.</i>	91
ANNOUNCEMENT: DANIEL STATS MEMORIAL PRIZE WINNER. <i>Klaus Dittmar, M.D.</i>	92

NUMBER 2, MARCH-APRIL, 1967

THE TEACHING HOSPITAL EXPERIENCE. <i>S. B. Gusberg, M.D.</i>	91
THE EFFECT OF PROBENECID ON SERUM LIPIDS: A STUDY OF DIABETICS AND	

NON-DIABETICS WITHOUT GOUT. <i>Melvin Jay Schwartz, M.D., Stanley Mirsky, M.D., and Walter Futterweit, M.D.</i>	96
SURGERY OF THE HAND IN RHEUMATOID ARTHRITIS. <i>Roger N. Levy, M.D.</i>	103
DUODENAL ULCER IN ABERRANT PANCREAS: CASE REPORT AND REVIEW OF LITERATURE. <i>R. Ashikari, M.D., Morton Roberts, M.D., and David A. Dreiling, M.D.</i>	111
DIFFUSE SMALL INTESTINAL ABNORMALITY DUE TO <i>GIARDIA LAMBLIA</i> WITH ROENTGEN AND CLINICAL REVERSIBILITY AFTER THERAPY: CASE REPORT, <i>Claude Bloch, M.D., and Lester R. Tuchman, M.D.</i>	116
EFFECTS OF 9,11-DIHALOGENATED CORTICOSTEROIDS IN VARIOUS TYPES OF ALOPECIA. PART I. CLINICAL STUDIES IN 32 PATIENTS. <i>Solomon I. Griboff, M.D., and Walter Futterweit, M.D.</i>	121
PITUITARY-ADRENAL RESPONSIVENESS IN PATIENTS TREATED WITH 16 α -METHYL-DICHLORISONE ALCOHOL. PART II. <i>Solomon I. Griboff, M.D., and Walter Futterweit, M.D.</i>	130
PSYCHIATRIC AFTERCARE: AN OPPORTUNITY AND A CHALLENGE. <i>Samuel L. Safirstein, M.D.</i>	135
SEXILE ARTHROSIS OF THE KNEE JOINTS: DEGENERATIVE OSTEOARTHRITIS. <i>Edgar M. Bick, M.D.</i>	146
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Editors</i>	
FAMILIAL POLYPOSIS.....	150
THIAZIDE-POTASSIUM CHLORIDE ILEAL STENOSIS.....	152
RECTAL VILLOUS ADENOMA—TEN YEAR FOLLOW-UP.....	155
RHABDOMYOSARCOMA WITH RESULTING ANEURYSM OF SUPERFICIAL FEMORAL ARTERY.....	160
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Khion, M.D., Editor</i>	
PURPURIC RASH AND PANCYTOPENIA IN AN ELDERLY FEMALE.....	161
THE MUSCLE BIOPSY PROGRAM AT MOUNT SINAI HOSPITAL: RESULTS OF A FIVE YEAR PROSPECTIVE STUDY. <i>Paul J. Anderson, M.D., S. K. Song, M.D., and Paul Slotwiner, M.D.</i>	171

NUMBER 3, MAY-JUNE, 1967

TRENDS IN NEW MEDICAL SCHOOLS

GUEST EDITOR: *Hans Popper, M.D., Ph.D.*

FOREWORD.....	208
---------------	-----

MEDICAL SCHOOL—COMMUNITY RELATIONS

MEDICAL EDUCATION: MEDICAL TECHNIQUE OR DISEASE CONTROL? <i>George James, M.D., M.P.H.</i>	209
THE MEDICAL SCHOOL-COMMUNITY EXPECTATIONS. <i>Cecil G. Sheps, M.D.</i>	216
THE WEDDING OF AN OFF-CAMPUS MEDICAL SCHOOL WITH A COMMUNITY OF MODERATE SIZE. <i>Lamar Soutter, M.D.</i>	222

COMMUNITY AND PROFESSIONAL PROBLEMS WITH A NEW MEDICAL SCHOOL. <i>Merlin K. DuVal, Jr., M.D.</i>	227
---	-----

MEDICAL SCHOOL—UNIVERSITY RELATIONS

THE UNIVERSITY IN MEDICAL EDUCATION. <i>DeWitt Stetten, Jr., M.D., Ph.D.</i> ...	232
A NEW INDEPENDENT MEDICAL COLLEGE SEEKS THE UNIVERSITY. <i>Glidden L. Brooks, M.D.</i>	237
GRADUATE EDUCATION AND MEDICAL EDUCATION: A SYNERGISM. <i>Irving L. Schwartz, M.D.</i>	242
AN INTEGRATED PROGRAM FOR PREMEDICAL AND MEDICAL EDUCATION—ITS IMPACT ON THE UNIVERSITY. <i>John A. D. Cooper, M.D., Ph.D., and Allen Lein, Ph.D.</i>	249

PROBLEMS OF NEW MEDICAL SCHOOLS, HERE AND ABROAD

MEDICAL EDUCATION FOR TOMORROW. <i>William F. Maloney, M.D.</i>	254
CHALLENGES TO NEW MEDICAL SCHOOLS. <i>J. R. Ellis, M.B.E., M.A. M.D.</i>	260
STARTING A MEDICAL SCHOOL IN A DEVELOPING COUNTRY: PROBLEMS AND APPROACHES. <i>Edward Grzegorzewski, M.D.</i>	267

STRUCTURE OF MEDICAL SCHOOLS IN VARIOUS COUNTRIES

A NEW ENGLISH MEDICAL SCHOOL AT THE UNIVERSITY OF NOTTINGHAM. <i>Professor G. M. Wilson</i>	274
CORRELATION BETWEEN THE TEACHING OF MEDICINE AND HUMAN BIOLOGY. <i>Professor Robert Debré</i>	280
DESIGN OF THE UNIVERSITY FOR MEDICAL AND NATURAL SCIENCES, ULM, GERMANY. <i>L. Heilmeyer, M.D.</i>	285
THE ORGANIZATION OF A MEDICAL SCHOOL. <i>Joseph Stokes III, M.D.</i>	295
NEW MEDICAL EDUCATION IN THE OLD SOUTHWEST. <i>Reginald H. Fitz, M.D. and Robert S. Stone, M.D.</i>	302
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Editors</i>	
LEIOMYOMA OF ILEUM PRESENTING AS FEVER OF UNKNOWN ORIGIN.....	309
CONGENITAL DIVERTICULUM OF BLADDER FLOOR.....	312
HAMARTOMA OF LUNG OBSERVED OVER A NINETEEN YEAR PERIOD...	315
CONGENITAL WEB IN LOWER ESOPHAGUS.....	319
TRAUMATIC PERFORATION OF RECTOSIGMOID IN NEONATE CAUSED BY THERMOMETER.....	323
TRAUMATIC PERFORATION OF RECTOSIGMOID IN NEONATE CAUSED BY DIGITAL STIMULATION OF RECTUM.....	327
THE SURFACES AND PLANES OF THREE-DIMENSIONAL COMPUTER-DRAWN VECTORCARDIOGRAM. <i>Louis Brinberg, M.D.</i>	331

NUMBER 4, JULY-AUGUST, 1967

TRENDS IN NEW MEDICAL SCHOOLS, PART II

GUEST EDITOR: HANS POPPER, M.D., Ph.D.

ARCHITECTURE OF MEDICAL SCHOOLS

PHYSICAL FACILITIES FOR THE EDUCATIONAL PROGRAM. <i>George T. Harrell, M.D.</i>	333
THE VERSATILE LABORATORY. <i>Edra L. Spilman, Ph.D.</i>	342
WHAT KIND OF ARCHITECTURE FOR EDUCATION FOR HEALTH? <i>Joseph Blumenkranz, A.I.A.</i>	348

THE STUDENT

STUDENT REVOLT AND OUR MEDICAL SCHOOLS. <i>Charles S. Davidson, M.D.</i>	356
A STUDENT'S VIEW. <i>Sidney R. Bloek</i>	361
PROPOSED CURRICULUM FOR THE MOUNT SINAI SCHOOL OF MEDICINE. <i>Tibor Barka, M.D., George Christakis, M.D., Howard L. Gadboys, M.D., David Koffler, M.D., and Fenton Schaffner, M.D.</i>	366

DISCIPLINES

PHYSICS, BIOLOGY AND MEDICINE. <i>Sergei Feitelberg, M.D.</i>	378
PATHOBIOLOGY-DEFINITION. <i>Donald West King, M.D.</i>	382
THE PSYCHIATRIST'S DILEMMA. <i>M. Ralph Kaufman, M.D.</i>	389
THE ROLE OF ILLUSTRATION IN MEDICAL EDUCATION AND MEDICAL PROGRESS. <i>Frank H. Netter, M.D.</i>	396

EPILOGUE

THE GOAL. <i>Hans Popper, M.D., and David Koffler, M.D.</i>	401
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THREE-DIMENSIONAL CONE-GENERATED COMPUTER-DRAWN VECTOR-CARDIOGRAMS. <i>Louis Brinberg, M.D.</i>	408
UNUSUAL PROBLEMS IN SURGERY. <i>Lewis Burrows, M.D., and Julius J. Leichtling, M.D., Editors</i>	
NEONATAL BOWEL NECROSIS AND PERITONITIS.....	410
BENIGN ESOPHAGEAL STENOSIS.....	417
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey Peek, M.D., Editors</i>	
INTUSSUSCEPTING COLONIC LIPOMA.....	425
MUOCOCELE OF APPENDIX.....	428
ULCERATING JEJUNAL MYOMA.....	430
RETICULUM CELL SARCOMA OF SMALL BOWEL.....	433
ADENOCARCINOMA OF GALL BLADDER.....	435

NUMBER 5, SEPTEMBER-OCTOBER, 1967

THE MEMBRANE LUNG: ITS EXCUSE, PRESENT STATUS, AND PROMISE. <i>E. Converse Peirce II, M.D.</i>	437
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MYASTHENIA GRAVIS AND THYROID DISEASE: CLINICAL AND IMMUNOLOGIC CORRELATION. <i>Kermit E. Osserman, M.D., Peter Tsairis, M.D., and Lee Burnett Weiner, Ph.D.</i>	469
INTUSSUSCEPTION IN ACUTE LYMPHOBLASTIC LEUKEMIA. <i>Moshe Haimov, M.D., Sheldon Freedman, M.D. and Mansho T. Khilnani, M.D.</i>	484
BACTERIAL DRUG RESISTANCE: CURRENT PERSPECTIVES. <i>R. J. Schnitzer, M.D.</i>	489
UNUSUAL PROBLEMS IN SURGERY. <i>A. Robert Beck, M.D., Lewis Burrows, M.D., and Julius J. Leichling, M.D., Editors</i>	
HYDATID CYST OF LIVER WITH ABSCESS, RUPTURE, EMPYEMA AND BRONCHO-HEPATICO-CYSTIC FISTULA.....	496
LUNG HERNIA.....	507
ABDOMINAL PAIN AND SHIFTING MASSES.....	512
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Khion, M.D., Editor</i>	
MALABSORPTION IN AN ELDERLY MALE.....	519
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Editors</i>	
REGIONAL ENTERITIS OF DUODENUM AND ILEUM.....	529
GASTRODUODENAL INTUSSUSCEPTION DUE TO ANGIOFIBROMA OF GASTRIC ANTRUM.....	535
CAVERNOUS HEMANGIOMA OF ILEUM.....	540
DIVERTICULITIS OF DESCENDING COLON SIMULATING CARCINOMA.....	543

NUMBER 6, NOVEMBER-DECEMBER, 1967

EMERGENCY LIVER RESECTION FOR PRIMARY CARCINOMA. <i>Richard G. Margoless, M.D., Barry Altman, M.D., M.S., F.R.C.S., and Allan E. Kark, M.D.</i>	547
MEDIASTINOSCOPY: EXPERIENCES WITH FIFTY CASES. <i>Paul A. Kirschner, M.D.</i>	559
POSTSYMPATHECTOMY NEURALGIA. <i>Allen Silverstein, M.D., and Julius H. Jacobson, M.D.</i>	574
CARCINOMA OF THE MALE BREAST. <i>Stanley Edelman, M.D.</i>	578
THE PORPHYRIAS. A CLINICAL REVIEW. <i>Leonard J. Lyon, M.D.</i>	587
COMPUTERIZATION OF SERIALS RECORDS IN THE MEDICAL SCHOOL LIBRARY. <i>Henry L. Lemkau, M.L.S.</i>	595
CHANGING PATTERN OF BACTEREMIA. <i>S. Stanley Schneiterson, M.D., Cecile Herschberger, B.S., and Manuel Alonzo, B.S.</i>	601
UNUSUAL PROBLEMS IN SURGERY. <i>A. Robert Beck, M.D., Lewis Burrows, M.D., and Julius J. Leichling, M.D., Editors</i>	
PRESACROCOCYGEAL CYST.....	606
MECONIUM PERITONITIS.....	609
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Khion, M.D., Editor</i>	
LIVER DISEASE IN AN ALCOHOLIC MALE.....	616
INDEX TO VOLUME XXXIV.....	629

In Memoriam

HENRY HORN

1906-1966

"For Lycidas is dead, dead ere his prime,
Young Lycidas, and hath not left his peer."

— from "Lycidas" by JOHN MILTON

With his death on August 16, 1966, The Mount Sinai Hospital has lost the services of a distinguished physician, his patients the ministrations of a warm and generous friend, and his colleagues and many friends the joy and youth of Henry Horn.

Dr. Horn was born in New York City on September 5, 1906, and attended the public schools in this city. He was graduated from New York University with the B.S. degree in 1928 and the M.D. degree in 1931. He interned at Bellevue Hospital and served his medical residency at Michael Reese Hospital in Chicago.

He came first to The Mount Sinai Hospital in 1934 and remained associated with the Hospital until his death. He served as a Fellow and Assistant in the Department of Pathology and in 1936 joined the Department of Medicine. He quickly made his mark by his acumen in clinical medicine and by his methods of bedside teaching, rising in rank so that he became Associate Attending Physician in 1953, a position he held until his demise. In addition to his activities at this Hospital, he served at various times as Assistant Attending Physician on the First Medical Division of Bellevue Hospital and Director of Laboratories and Attending Physician at Knickerbocker Hospital.

Since 1941 Dr. Horn maintained a formal teaching affiliation with Columbia University College of Physicians and Surgeons, serving as Instructor in Cardiology and subsequently as Assistant Clinical Professor of Medicine. From 1949 to 1955 he was Director of Intern Education at Knickerbocker Hospital. In 1965 he was appointed Associate Clinical Professor of Medicine at the newly formed Mount Sinai School of Medicine.

He was a member of many scientific and medical societies including the American College of Physicians, American Association of Pathologists and Bacteriologists, New York Academy of Medicine, New York Pathological Society, American Heart Association, Harvey Society, Pan American Medical Association, American Medical Association and its state and local affiliates. He was a member of Alpha Omega Alpha, the Alumni Societies of The Mount Sinai Hospital and Bellevue Hospital. He served as a member of the Medical Board of The Mount Sinai Hospital and as chairman of its Pharmacy and Therapeutics Committee.



HENRY HORN, M.D.
1906-1966

During World War II Dr. Horn served with The Mount Sinai Hospital Unit (Third General Hospital) in the North African and Southern European campaigns, attaining the rank of Lieutenant Colonel. He is survived by his wife, the former Ruth Eichel, a graduate of the Mount Sinai School of Nursing, and his son David.

Henry Horn was devoted to clinical medicine and he practiced his art as a professional in his private office and at the hospital. His ward rounds were exercises in careful physical diagnosis, in the application of his knowledge of morbid anatomy to clinical problems and in the utilization of his intuitive clinical judgement. He taught his staff the proper clinical approach to the patient's problems. A man of action, he lectured on the need for prompt attention to the patients' needs. He brooked no delay. Although interested in the broad discussion of disease processes, he was partisan to the immediate solution of the problem at hand. Utilizing wit and humor, he was the catalyst for electrifying ward rounds with his familiar "What are we going to do about it TONIGHT?"

Henry's gentlemanly ways, his disarming friendliness, his keen wit and his high moral standards—these will be sorely missed. He lives on in "the acts of goodness he performed and in the hearts of those who cherish his memory." He was the apotheosis of the Physician and hath not left his peer.

SAMUEL K. ELSTER, M.D.

for the

EDITORIAL BOARD

Mortality Among Young Narcotic Addicts

PERCY MASON, M.D.

Almost every physician, at one time or another, comes into contact with problems of addiction (1). Narcotic drug addiction poses serious sociological and psychiatric problems. It also presents serious health hazards to the individual addict in terms of localized or generalized infections, hepatitis, etc., as well as the possibility of death from an overdose. It is estimated that 1% of the addict population dies each year from overdose (2).

The Medical Examiner of the City of New York stated that for the calendar year 1953 there were 541 deaths due to alcoholism, while at the same time there were 100 deaths due to drug addiction (3). These figures assume ominous portent when we consider that there were approximately 350,000 alcoholics in the New York metropolitan area, but only about 20,000 addicts according to estimates of that time. This is a rate of only a little over 1.5 per 1,000 for alcoholics, but 5 deaths per 1,000 for addicts, indicating that the death rate of addicts is three times that of alcoholics.

Pescor (4) states that among the 4,766 addicts who were hospitalized at the U. S. Public Health Service Hospital at Lexington, Ky., between January 1, 1936 and December 31, 1940, 9.7% had died by the time his investigation was terminated December 31, 1941. He also states that "a number of drug addicts start using drugs because of poor health, and by virtue of poor health are likely candidates for death." Poor health as a cause of addiction is rare today, and certainly was not the cause of addiction in the youthful population described in this report; besides, the prolonged use of narcotics in painful and chronic illnesses is not considered a true addiction.

Trussel et al (5) studied 247 first admissions of adolescent addicts of both sexes to Riverside Hospital, and found that three years later 11 had died. He remarks: "the eleven deaths constitute a very high rate for the group in question. Some recorded information indicates that the majority were due to overdose of narcotics." Duvall et al (6) report 52 deaths among the 453 addicts in their sample, 19 occurring in the age group under 30 (16 per 1,000), and 33 in the group over 30 (30.7 per 1,000), which was higher than the rates for the corresponding population groups in New York City in the years studied. "Furthermore, 15 of the 19 (78.9%) deaths for those under 30 were directly attributable to drug usage." Finally, O'Donnell (7) found 37 deaths due to narcotic addiction in a sample of 266 addicted Kentucky residents. One third of the original life expectancy of this sample was lost among the male subjects, while among the females the loss was about one fifth.

From the Department of Psychiatry, Institute of Psychiatry, The Mount Sinai Hospital, New York, N. Y.

Presented in part at the National Academy of Sciences-National Research Council, Committee on Problems of Drug Dependence, New York, N. Y., February 10, 1966. Based upon observations made during 1952-1962 at Riverside Hospital, New York, N. Y.

All cited sources, then, seem to agree that the mortality among narcotic drug addicts is high.

METHODOLOGY

The present study is based on the population of Riverside Hospital in New York City (8), which admitted young narcotic addicts of both sexes from the New York metropolitan area. The patients were between the ages of 15 and 21 at the time of their first admission. The majority came from a socially, economically and educationally deprived background. They all used heroin in differing amounts and with varying frequency, but sufficient to be considered addicted. About one third used other drugs, notably barbiturates, at the same time.

The cause of death was ascertained whenever possible for all patients admitted between July 1, 1952, when the Hospital was opened, and October 31, 1962, when this study was concluded. Only deaths substantiated by official Medical Examiner's reports or Health Department death certificates were included in this study. In one case a statement from the U. S. Consul in a foreign country was accepted.

The cause of death was recorded as it appeared on the official document. In some cases there was reason to believe that death from overdose had been overlooked by the authorities; this seems to be specially true for the diagnoses "visceral congestion" and "aspiration bronchopneumonia" which account for six cases.

POPULATION

A total of 2,743 first admissions, male and female, was recorded during the period of study, among whom 74 deaths occurred; 66 in males and 8 in females. Of the total number of male deaths, 39 males died from overdose of narcotics; 27 males died from other causes. Four females were represented in each of these categories (Table I). The female sample is considered too small statistically for any valid conclusions.

Data are available concerning the racial origin of a sample of these patients: of 1,617 admissions from 1952 to 1958 approximately one third each were White, Negro, Puerto Rican (8). Table I indicates a much higher mortality due to overdose among Negro than among White and Puerto Rican. The Negro mortality from overdose is 70.8%, while deaths due to other causes account for 29.2%. The same categories among white and Puerto Rican account for 52% and 48% of deaths respectively.

The breakdown of "other causes" of death is presented in Table II. It is of interest to note that although about one third of the patients used barbiturates, not one death due to this drug was recorded. The other frequently mentioned causes of death among addicts—tetanus, malaria, bacterial or mycotic endocarditis—were also absent. In only one case alcoholism alone was given as cause of death: this case of alcoholic hallucinosis occurred in a 28 year old Negro, who died nine years after his last discharge from the hospital. In five others,

all males, the diagnosis of acute or chronic alcoholism appeared on the death certificate in addition to the diagnosis of overdose.

The fact that all patients had a psychiatric work-up made it possible to add a psychiatric diagnosis to the medical diagnosis of drug addiction. The diagnostic standards and nomenclature of the American Psychiatric Association were used throughout. Table III indicates the figures concerning male patients. Schizophrenia was most frequently of the chronic undifferentiated type. Florid secondary manifestations were seen infrequently (Case 1 described in another paper (9) was included in the present study).

In evaluating these data, the sample referred to above (8) indicates that approximately two-thirds of the patients had personality disorders, one fourth had schizophrenia, and a small minority were diagnosed as psychoneurosis. Approximately 85% were males. Although there were more personality disorders than schizophrenia in the total group, the number of deaths due to overdose and to other causes was approximately the same. However, a larger percentage of those with schizophrenia died, and these died generally of overdose.

Of those who died from overdose 18.6% died within seven days after discharge; 30.2% in less than a month; 48.8% within three months, and 69.7% in less than a year's time. Such high mortality in such a short time after discharge from the hospital seems to indicate a very high vulnerability of these patients at the time when their physical condition following detoxification at the hospital is good, and when they have been warned that they cannot with impunity resume their former dosage of heroin, their tolerance being lower. But since the addict is "greedy," this knowledge does not deter him. All patients were routinely advised and expected to attend the After Care Clinic, but their attendance was sporadic and irregular. Different means were employed to increase the attendance—phone calls, letters, contacts with relatives, pressure from probation officers, etc.—but the results were not satisfactory. Would a more compulsive structure of the After Care Clinic have improved attendance? Would better contact and supervision at the Clinic have avoided some of these deaths so soon following discharge?

The annual death rate per 1,000 among the 15 to 21 age group in New York City is approximately 0.99 (10). On that basis one would have expected about 27 deaths in the 2,743 cases within the year following discharge. Actually 69.7% of the 74, or about 51 or 52 died within the year, so that the observed deaths were about twice the expected number.

CLINICAL OBSERVATIONS

Death occurred under varying circumstances. Some patients were found on rooftops, in hallways, or at their own home or that of a fellow addict. Some died after having been brought to a hospital for emergency treatment. No statistics are available as to the frequency of overdose, but the general impression among our patients was that almost every addict has experienced it at least once with different degrees of severity. Addicts themselves know of this possibility and are fatalistic about it: overdose is an occupational hazard. Every addict is

prepared to render some degree of emergency treatment to a friend who has an overdose. Keeping the subject walking and awake, and a "salt shot" is standard procedure. (The rationale behind the "salt shot" is speculative. A "salt shot" consists of a liberal amount of table salt dissolved in water and administered either subcutaneously or intravenously. It may well be that the addict is seeking to imitate the saline infusion used by physicians in such an emergency. It is also possible that such a procedure provides a painful stimulus to combat the impending coma.) It is difficult to say how effective this treatment is as compared to hospital treatment; statistics concerning both procedures are lacking. It is widely known among those working in the field of addiction that death may follow discharge from the hospital after seemingly successful emergency treatment. The following example is illustrative:

W. B. was treated for heroin overdose in the emergency ward of a hospital. He responded to treatment and was discharged six hours after regaining consciousness. He lapsed into coma three hours later and died shortly afterwards at home.

The wisdom of such an early discharge from the hospital should be questioned. It may be better and sounder medical practice to keep these patients under observation in the hospital for 24 hours from the time they regain consciousness.

SELF-DESTRUCTIVE DRIVES

One may wonder why addicts persist in injecting into themselves a substance of unknown composition and potency. There is no effective way of judging the content of a "deck" which usually contains heroin, lactose, quinine and other adulterants (2, 9), but which is known to be potentially lethal. Repeatedly taking such a risk must be related to self-destructive drives. Suicide was mentioned in two of the death certificates. It is quite possible that more suicides have occurred without being recognized as such. There were several instances, in which suicide was strongly suspected but not proven, as in the following case:

G. B. had been ejected from home by his mother as soon as she became aware of his addiction. His own efforts as well as those of the social worker toward reconciliation were of no avail. A great deal of time in his therapy was spent discussing the patient's plan to confront his mother with his urgent need for her. Although he had been cautioned against it, he went directly to her home upon his discharge from the hospital. The mother literally slammed the door in his face. He was found dead of an overdose a few hours later.

It is an unresolved question as to whether the suicidal behaviour of the addict has its roots in underlying chronic depression, or in masochistic character structure. K. Menninger advanced the concept of chronic suicide years ago (11). Such "suicide on the installment plan"—be it by starvation, physical neglect, administration of noxious substances (as in addictions), etc.—certainly could be suspected in our patients, although very few of them would admit to

these tendencies. Much more frequently one encounters the notion "I can take it or leave it," or "I am not hooked," when the patient is patently in a state of physical and psychological dependence. Such attempts at mastery are frequently encountered, and it is important not to permit such omnipotent illusions to persist.

At which point does an overdose or suicide intervene? Chein et al (12 p. 356) state that suicide occurs early in the course of the readdiction cycle when there is remorse, guilt, and discouragement over failure to remain abstinent and when the addict becomes aware of "the difficulties of being an addict in our society." From observations gathered at Riverside Hospital one has the impression that the well being which follows detoxification enhances the feelings of omnipotence, which then suffer a severe blow when confronted with the unchanged reality outside of the protective hospital setting. It must also be said that some therapists unconsciously aid and abet such Pollyannaish attitudes. It satisfies the therapist's own omnipotent needs to see the patient well, confident and hopeful, with complete disregard for the reality of his lifelong difficulties.

Chein et al (12 p. 3) says: "H is for haven; H is for hell; H is for heroin." An addict-poet wrote:

It's a thrill I could never express
And I know some day it will lay me to rest,
For heroin you are my only one.

CONCLUSIONS

Seventy-four deaths occurred among a group of 2,743 young heroin addicts aged 15 to 21, admitted to Riverside Hospital between 1952 and 1962. More than half of the deaths were due to overdose of heroin, and such fatal overdose occurred within one year of discharge from hospital in two-thirds of cases. These deaths represent a high mortality rate for this age group.

Careful observation of addicts after hospital discharge is important, as evidenced by the high death rate during the immediate post-discharge period.

Emergency treatment in cases of overdose should be followed by hospital observation for approximately 24 hours after the patient's apparent recovery.

TABLE I.—*Cause of Death by Race, Both Sexes*

	Overdose		Other Causes		Total Deaths
	Number	%	Number	%	
White.....	15	51.7	14	48.3	29
Negro.....	17	70.8	7	29.2	24
Puerto Rican.....	11	52.4	10	47.6	21
Total.....	43	58.1	31	41.9	74

TABLE II.—*Causes of Death other than Overdose among 74 Narcotic Addicts, as Recorded on Death Certificates*

	Male	Female	Total
Accident.....	10		10
Homicide.....	4	1	5
Suicide.....	1	1	2
Congestion of viscera*	4		4
Bronchopneumonia, aspiration*	2		2
Hepatic failure.....	2		2
Alcoholic hallucinosis.....	1		1
Septicemia.....	1		1
Pancreatitis, acute.....	1		1
Meningitis, influenzal.....	1		1
Rheumatic heart disease.....		1	1
Sarcoma, kidney.....		1	1
Total.....	27	4	31

* See text discussion suggesting that these deaths may also be due to Overdose.

TABLE III.—*Psychiatric Diagnoses by Cause of Death and Race of 66 Consecutive Deaths among Male Narcotic Addicts*

	Overdose (39 Deaths)				Other Causes (27 Deaths)			
	W	N	PR*	Total	W**	N	PR	Total
Schizophrenia.....	6	5	5	16	3	0	0	3
Personality disorder.....	9	9	4	22	7	6	8	21
Psychoneurosis.....	0	0	0	0	1	0	0	1
Total.....	15	14	9*	38	11**	6	8	25

* 1 PR undiagnosed

** 2 W undiagnosed

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Spontaneous Disappearance of Pulmonary Metastases in Hypernephroma

Final Report of Twenty Year Follow-up after Nephrectomy

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This case was first presented in the *Journal of Urology* in 1948 by Mann(1). The report aroused considerable interest and has been referred to many times in the literature. The unusual biological phenomenon and its great clinical importance prompted us to publish the present study.

At the time of the original report, the patient was four years post nephrectomy for hypernephroma (Fig 1a, 1b). A preoperative chest x-ray had shown bilateral "cannon-ball" metastases (Fig 2). No lung biopsy was obtained; no radiotherapy was given either pre- or postoperatively. After leaving the hospital, the patient appeared to deteriorate and in summer 1945 frank hemoptysis occurred. Thereafter, his general condition improved with gain in weight and strength. Chest x-ray 22 months postoperatively disclosed complete disappearance of the pulmonary nodular shadows (Fig 3). The only abnormality noted was some linear fibrosis in the right lung.

The patient was seen at regular intervals and remained asymptomatic except for a left inguinal hernia with several episodes of incarceration for which surgery was not performed. Repeated chest x-rays and bone surveys were consistently normal. In 1955 physical examination for an upper respiratory infection revealed no metastases and chest x-rays were again negative (Fig 4). The patient continued to lead a normal life until March 1963 when he died following a cerebrovascular accident. No autopsy was obtained. At the time of death the patient was 82 years of age and had lived exactly twenty years after the renal extirpation.

Although there was no histological diagnosis of the lung lesion, there is no doubt that the lung deposits were metastatic, as interpreted by all established and accepted radiological criteria and as read by various reputable radiologists.

REVIEW OF LITERATURE

There are relatively few reports in the literature describing the spontaneous disappearance of pulmonary metastases in hypernephroma treated by nephrectomy (2-5).

Spontaneous disappearance can even occur without surgical extirpation of the original renal neoplasm. Grabstald's patient (6) was subjected to exploratory thoracotomy for pulmonary nodules. Biopsy of widespread pleuropulmonary implants showed renal cell malignancy. Intravenous urography disclosed the right kidney as the probable source of the metastatic tumor. Nephrectomy was not performed, and repeated roentgenograms of the chest

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showed spontaneous regression with no evidence of metastatic disease up to five years after thoracotomy. However, at this time the patient died. The cause of death was unknown and no autopsy was obtained.

Bumpus, Jr. (7) in 1928 reported the case of a patient who underwent nephrectomy for hypernephroma. A preoperative chest x-ray was normal. Fifteen months postoperatively the patient developed cough and hemoptysis. Chest x-ray showed the presence of multiple metastatic nodules which disappeared a few months later.

A case similar to the preceding was reported in 1937 by Beer (8). In Beer's case, too, the pulmonary metastases appeared after nephrectomy for hypernephroma. Five months later the patient's chest x-rays were normal, although no specific therapy had been given.

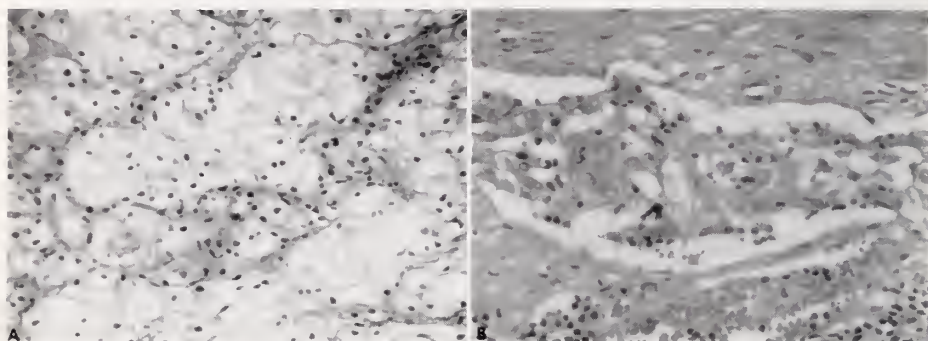


FIG. 1a, 1b. Malignant Grawitz tumor. No invasion of large veins is found, but microscopically the small veins and lymphatics appear invaded (December 24, 1943, $\times 200$).

Hyman (9) stated that metastasis—especially the presence of a single metastatic lesion—is no contraindication to nephrectomy.

Hallahan's patient (10) had preoperative chest x-rays showing multiple bilateral metastases. After nephrectomy for hypernephroma the metastases spontaneously disappeared. The patient died three years later at the age of 78 from cardiovascular disease. An autopsy showed no metastases.

Jenkins (11) reported regression of pulmonary metastases following nephrectomy for hypernephroma. His patient had a positive preoperative chest x-ray and in the first report (1959) this author presented an eight year follow-up. In the final report (1965) Jenkins (12) stated that the patient developed a recurrence of clear cell carcinoma in the wound ten years following the original operation, but the chest x-rays remained negative. The patient then exhibited a massive tumor recurrence at the original site for which he received radiotherapy. He died about 13 years after the nephrectomy. The chest x-ray before death was negative for metastatic disease. Autopsy findings revealed recurrent hypernephroma at the operative site. Macroscopically, the lungs showed only bronchopneumonia, but on microscopic section, areas of viable



FIG. 2. Chest x-ray shows a number of nodules measuring from 1 to 4 cm in diameter scattered through both lungs. The appearance is that of a metastatic neoplasm (December 9, 1943).

FIG. 3. Reexamination of chest shows complete disappearance of the nodular deposits previously described in lungs. Only abnormality noted is some linear fibrosis in right lung (September 1, 1945).

FIG. 4. No abnormality of heart and lungs is noted. There is no evidence of metastases (March 22, 1955).

renal clear cell carcinoma were seen, encapsulated by dense hyalinized connective tissue.

DISCUSSION

Hypernephroma is biologically an unusual neoplasm. Its behavior is unpredictable as to the rate of progression.

Hultquist (13, 14) described the occurrence of self-healing hypernephromas in the kidney. He believes that certain cortical scars are caused by regressing hypernephromas. The spontaneous disappearance of metastases from hypernephroma is probably due to the intrinsic "frailty" of this tumor.

Zak (15), reporting on five tumors, confirmed Hultquist's findings and interpretation. He emphasized the common occurrence of spontaneous regression of cortical renal cancers particularly of the clear cell variety. In the typical large hypernephroma necrobiotic and reparative phenomena take place, which account for its variegated cut surface. Thus, the process of partial or complete healing of small cortical renal tumors results in cortical scars.

Carlson and Ockerblad (16) reported the case of a patient with unoperated hypernephroma who survived ten years after diagnosis.

There is an inherent individual reaction to metastatic dissemination (17). Sometimes at operation, invasion of the renal vein or vena cava is found, yet the patient may outlive those in whom no gross evidence of spread is noted. One may therefore assume that although the body is probably showered with tumor cells via the blood stream, clinical metastases do not necessarily develop or may occur later. Melicow (18) states that "not all [tumor] emboli survive but [some] because of favorable physiochemical biologic factors tend to form a colony."

There is considerable speculation on the subject of regression of pulmonary metastases in hypernephroma. Hallahan (10) and others have mentioned a few of many possible explanatory theories.

Complete regression of all tumors occurs in about one out of 100,000 patients (19).

There is the possibility that metastatic deposits may undergo progressive changes such as fibrosis and hyalinization and even calcification and ossification (14). This theory would certainly account for the autopsy findings in Jenkins' case (12). In our case the persistent fibrosis evidenced in the right lung field might be interpreted in this sense.

Pulmonary metastatic emboli, which lodge in the small end vessels in the lungs may become surrounded by hyaline thrombi which subsequently undergo organization. This would lead to loss of viability, atrophy and autolysis of cancer cells (20).

Immunological reactions of an antigen-antibody type may explain the regression of metastases (21, 17).

Recently, Bloom (22) in Great Britain has studied both experimentally and clinically the hormonal dependence of renal tumors. An unexplained change in a patient's hormonal status may prove to be related to the disappearance of pulmonary metastases in hypernephroma.

CLINICAL APPLICATION AND CONCLUSIONS

Regression of pulmonary metastases in hypernephroma is a well recognized but rare phenomenon for which no satisfactory explanation has been found. Although various theories have been advanced to explain this unusual happening, no clinical or laboratory data are presently available to predict such fortunate prognosis.

Humphreys (23) believes nephrectomy has not influenced the growth of metastases and should not be performed except in selected cases.

It has been the experience of the authors and others, that the follow-up results for nephrectomy with multiple pulmonary metastases have been extremely poor. However, in the presence of a single lung metastasis removable by lobectomy, renal extirpation is indicated. There have been a few such cases successfully treated.

Barney and Churchill (24) reported the long term survival of a patient with renal cell carcinoma and a solitary lung metastasis who was treated by nephrectomy followed fifteen months later by partial lobectomy. Potampa (25) reported a five year cure after nephrectomy and subsequent staged removal of bilateral pulmonary metastases. Grabstald (6) similarly mentioned a few cases where nephrectomy for renal cell carcinoma was followed by removal of the metastatic lesions but he also states that he knows of no case of disappearance of skeletal metastases after nephrectomy.

There are only occasional indications for nephrectomy in hypernephroma in the presence of multiple pulmonary metastases, i.e. pain, severe hemorrhage and infection.

SUMMARY

A patient with renal cell carcinoma and lung metastases discovered preoperatively underwent nephrectomy. The lung metastases disappeared spontaneously 22 months postoperatively and the patient remained free of symptoms to his death which occurred 20 years later at the age of eighty-two. The patient died following a cerebrovascular accident.

The literature on the spontaneous disappearance of pulmonary metastases in hypernephroma has been reviewed, and the many possible theories on this interesting subject have been discussed.

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Clinical Evaluation of Patients with Neuromuscular Disorders

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Introduction

Recent dramatic advances in the study of neuromuscular diseases have greatly increased the awareness of the clinician of this group of disorders, particularly the myopathies. As a result of the techniques of neurophysiology applied to the patient, and of histology, histochemistry, biochemistry and electronmicroscopy applied to the muscle biopsy, our diagnostic capabilities have been considerably expanded. Patients who previously were not candidates for investigation other than physical examination can now be studied intensely. The information obtained is essential not only for increased understanding of these disorders, but also for diagnosis and management. As a result of our neuromuscular program at Mount Sinai Hospital we have become aware of a broad spectrum of systemic diseases which may present as neuromuscular disorders. Within this group, specific diagnostic studies to determine the underlying disease must be undertaken. While at present specific therapy may be possible for only a limited number of neuromuscular disorders, often an accurate prognosis may be of equal value in management of the patient.

The rapid expansion of diagnostic techniques raises the possibility that the clinician may be so awed with their capabilities that he resigns himself to ordering a battery of nonspecific studies and awaiting the "answer" from the laboratory. However, most of the techniques mentioned are still in the early stages of their development and any tendency of the clinician to relinquish his role in the clinical evaluation of the patient is not only premature but detrimental both to the patient and to the development of the newer methods. If these techniques are to continue to develop to give additional meaningful information to increase our understanding, they must be combined and correlated with a standardized clinical evaluation of the patient. The approach to the patient in making that evaluation is the subject to be discussed here.

Definitions

Neuromuscular Disorder. A disease manifested by symptoms or signs which can be attributed to altered function of one or more of the following: The lower motor neuron (anterior horn cell or cranial nerve nuclei), the root or peripheral nerve emanating from the neuron, the neuromuscular junction, the skeletal muscle fibers innervated by the neuron and the interstitial tissues of the skeletal muscle.

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Myopathy. A disease affecting skeletal muscle fibers or their interstitial tissues which is not secondary to disease of the central or peripheral nervous system.

Muscular Dystrophy. A genetically determined myopathy, regardless of course or age of onset. This term has, for many years, been restricted to describe the classical progressive dystrophies of infancy, childhood and early adulthood, but with the recent discoveries of new genetically determined, congenital myopathies such as nemaline myopathy, myotubular myopathy, central core disease, and McArdle's disease, its application must be expanded.

Approach To The Patient

General Considerations

Many tabulations of factors to be considered in the differential diagnosis of myopathies have been compiled and most are of little use at the bedside because, first, they often rely on laboratory information not available at the bedside and thereby deemphasize the importance of the examination and, second, they assume the diagnosis of myopathy (as opposed to neuromuscular disease) has already been made, where in fact this is often the major difficulty. From the definition of myopathy it is apparent that there is an element of exclusion involved, i.e. one must determine that the symptoms or findings are not due to disease of the central or peripheral nervous system. Only then can one make the anatomic localization of myopathy. In order to do this, in addition to the specific examinations enumerated here, a complete neurological examination including examination of mental status, cranial nerves, motor system, reflexes and sensory status must be performed. The goal at the bedside is to classify patients according to broad anatomic categories, within which further classification may be possible on clinical grounds alone. Subsequently appropriate further studies may be undertaken to establish more precise localization and the etiology. The categories used are as follows:

1. Diseases of the nervous system
 - a) Myelopathy
 - b) Peripheral Neuropathy
 - c) Myeloradiculoneuropathy
2. Myopathies
 - a) Dystrophy
 - b) Myositis
 - c) Other myopathies
3. Myasthenic Syndrome
4. Neuromuscular diseases not further localizable

Diseases of the Nervous System

Myelopathy. This includes amyotrophic lateral sclerosis, reserved for patients showing the complete syndrome of anterior horn cell disease (fasciculations), lateral column disease (abnormal reflexes) and absence of sensory changes. All other patients showing only part of this syndrome, or showing other signs at-

tributable to the spinal cord, such as sensory levels or paraplegia, are classified as "other myelopathies."

Peripheral Neuropathy. This includes patients with distal, glove and stocking distribution of paresthesias and/or sensory loss, most of whom also have depressed or absent reflexes. Weakness in the same areas may be present or absent. Also included will be some cases of weakness with no sensory changes, but these must be differentiated from similar syndromes which may be produced by disease of the central nervous system or of muscle.

Myeloradiculoneuropathy. This includes patients with evidence of spinal cord, root and peripheral nerve disease as well as those patients with symptoms and signs indicating disease at one of these levels that cannot be further localized by clinical examination.

Myopathies

Dystrophy. Many patients with dystrophy can be diagnosed on clinical grounds alone. This is particularly true of those with diseases such as pseudohypertrophic, facioscapulohumeral, limb-girdle and myotonic dystrophy. For in these categories the total clinical picture including family history, mode of inheritance, onset, course and physical findings is more or less distinctive. Thus a patient with all the features of myotonic dystrophy presents little difficulty in diagnosis. However, with the other dystrophies mentioned thus far, cases which have features of more than one type are common. With regard to the more recently described congenital myopathies, their clinical features are not distinctive, and diagnosis depends on characteristic muscle biopsy findings (e.g. the centrally located histological and histochemical abnormality of central core disease, the presence of rod-like bodies in nemaline myopathy, and the absence of muscle phosphorylase and presence of excess muscle glycogen in McArdle's disease). It should be mentioned that cases filling all the criteria of any of the dystrophies may be encountered in the absence of a positive family history, i.e., spontaneous cases of all types are known to occur.

Myositis. If a diagnosis of myositis is to be made on clinical grounds the syndrome must be defined exclusive of histologic abnormalities. We restrict it to those cases of myopathy accompanied by a significant history or by findings of muscle pain and tenderness. Skin changes may be present or absent.

Other Myopathies. Included here are all other cases of myopathies which do not fulfill the clinical criteria of the previous two groups. The majority of cases of myopathy seen on an active general neurological service fall into this group. Further classification depends on laboratory and biopsy information. Rarely, as in the case of multiple attacks of periodic paralysis, a more specific diagnosis may be suspected on clinical grounds.

Myasthenic Syndrome

Most cases of this disorder of the myoneural junction present fairly characteristic pictures of ocular, bulbar, or limb fatigueability with daily variations so that the diagnosis can be strongly suspected at the bedside. However, final

proof depends on the response of the patient to drugs known to affect neuromuscular transmission, such as Tensilon.

Neuromuscular Diseases Not Further Localizable

The best example of this group is the "floppy infant" in which the infant shows congenital generalized flaccid weakness, without definite evidence of nervous system disease (such as fasciculations). In such cases the major differential diagnosis is between disease of the spinal cord (Werdnig-Hoffmann's disease) and myopathy. The final answer depends on findings of EMG and muscle biopsy.

A somewhat similar situation may rarely be encountered in older children or adults; i.e. a relatively rapid (hours to days) onset of flaccid quadriplegia with depressed or absent reflexes and no other findings. In this instance the major differential diagnosis is usually between a polyneuropathy (Guillain-Barré syndrome) and a type of periodic paralysis (e.g. paralysis associated with hypokalemia or hyperkalemia or idiopathic myoglobinuria). As in the case of the "floppy infant," the diagnosis depends on further laboratory studies.

History and Examination

History. Only a limited number of complaints are referable to the neuromuscular system: (a) weakness, (b) wasting or atrophy, (c) pain or tenderness (d) abnormal movements (e.g. fasciculations, dyskinesias) (e) other types of impaired function (e.g. myotonia) and (f) sensory disturbances.

Weakness (a) is the most common of these and much can be learned about the distribution of involvement prior to examining the patient. Thus a patient with proximal weakness of the legs may complain of difficulty in climbing stairs or rising from a chair, while one with proximal arm weakness may complain of difficulty in combing his hair or shaving. Similarly, a patient with primarily distal weakness of the upper extremities may complain of difficulty with fine manipulations of the hand or turning a key; one with a foot drop may state that his toes "get caught" on low steps or curbs, one with involvement of bulbar muscles may complain of dysarthria or dysphagia. Though of value in establishing the distribution of involvement, the complaint of weakness is obviously of no value in determining which of the neuromuscular diseases one is dealing with, since it may be caused by any one of them. The same is true for the complaint of wasting or atrophy (b). Pain or tenderness (c) may be very helpful and indicative of a myopathy, more specifically a myositis, but must be differentiated from dysesthesia. Abnormal movements (d) usually indicate nervous system disease, and may allow for more specific localization, such as the anterior horn cell in the case of fasciculations, or the cerebellum or basal ganglia in cases with characteristic defects of ataxia and tremor.

In the case of myotonia (e), the impairment of skeletal muscle relaxation following voluntary contraction, patients may complain of difficulty in releasing objects from their grasp, such as in shaking hands. Though the phenomenon must be verified by examination, it can be strongly suspected by the history, and if present is the most reliable single diagnostic factor for localizing the

process to muscle; it indicates myotonic dystrophy or one of the benign myotonic syndromes, such as myotonia congenita or paramyotonia congenita. Recently the phenomenon has been increasingly reported with another type of myopathy, periodic paralysis associated with abnormal serum potassium levels.

Sensory disturbances (f) are of obvious significance in the differential diagnosis, as they indicate that the patient has nervous system disease which may be peripheral or central, regardless of whatever else is present. The history should also include a search for other complaints sought in any neurological evaluation, such as changes in mental function, loss of consciousness or visual disturbances.

Associated factors in the history not related directly to the neuromuscular system but of potential diagnostic significance include skin changes, joint changes, presence of Raynaud's phenomenon, weight loss (particularly if not associated with the complaint of dysphagia), fever, exposure to toxic substances including medications, clinical course and a detailed family history. This information may suggest that one is dealing with a neuromuscular disease associated with rheumatoid or collagen disease, endocrinopathy, occult neoplasm, or one with a genetic basis.

Examination. What is required is a complete neurological examination in which particular attention is given to systematic testing of all possible movements at all joints, including those of the neck and jaw. Some attempt is made to grade the degree of weakness, based on a modification of the system outlined by the Medical Research Council of Great Britain (War Memorandum No. 7). As modified, +5 indicates normal power, +4 mild weakness, +3 severe weakness but ability to maintain movement against resistance and gravity, +2 inability to maintain movement against gravity, +1 no gross movement of joint but only visible muscle contraction on attempted movement, and 0 for no movement or visible muscle contraction. In practice, the designations of normal, mild weakness and severe weakness for each joint movement are sufficient. Whenever possible, physiologic movements, such as rising from a chair or squat, or hand grasp, should be tested in addition to the standard evaluation of strength against the examiner's resistance. If the findings are then systematically reported for each joint movement in a convenient tabular form one gets an excellent picture of the distribution of weakness without recourse to such terms as "proximal more than distal." Much emphasis is usually placed on the distribution of weakness and in fact this can often be useful. Many disorders have patterns of distribution which are more or less characteristic. However, even with the larger categories of nervous system disease and myopathies, the distinction cannot be based on distribution alone. The often repeated statement that myopathies cause proximal weakness and neuropathies cause distal weakness is contradicted by many clinical examples, such as myotonic dystrophy which usually first affects distal muscles, and the proximal muscle atrophy and weakness secondary to spinal cord disease described by Kugelberg and Welander. There are also many examples of patients whose weakness is generalized, and attempts to fit them into proximal or distal syndromes is unrealistic. In this regard care should be taken to evaluate muscle strength within the frame-

work of the normal ability for the movement being tested. For example, weakness of shoulder abduction may be more dramatic during the examination, in that the outstretched arms may be easily depressed by the examiner, but this does not mean that the same patient may not have an even greater loss of normal power for finger abduction, even though weakness here produces a much less dramatically demonstrated physical finding.

In addition to weakness, the examination should include specific testing for depressed or absent reflexes, abnormal reflexes, atrophy, fasciculations, myotonus, muscle tenderness, sensory abnormalities, palpable peripheral nerves, ataxias and abnormal movements.

Laboratory Studies

With the exception of the muscular dystrophies, cases falling into any of the broad categories previously outlined may be associated with or secondary to a wide variety of systemic disorders. Among those disorders most commonly encountered presenting as neuromuscular syndromes are (a) so-called "auto-immune diseases" (rheumatoid arthritis, lupus erythematosus, scleroderma, polyarteritis, dermatomyositis), (b) neoplasms (particularly lung) and (c) endocrinopathies (especially thyroid disease and diabetes). These diseases may present with all the clinical characteristics of a disease of the nervous system or a myopathy or combinations of both. A typical myasthenic syndrome may be encountered associated with lung carcinoma. Thus appropriate studies must be performed to rule out these causes of neuromuscular diseases.

Within the dystrophic group the congenital dystrophies, as we have seen, depend on specific muscle biopsy findings. Those related to abnormalities of glycogen breakdown (e.g. Mc Ardle's disease or limit dextrinosis) may be indicated by failure of blood lactate to rise after exercising a limb under ischemic conditions, but in order to determine which glycogen storage disease is present, biochemical studies on biopsied muscle must be performed. For the remainder of the dystrophies, laboratory studies, such as serum enzymes and muscle biopsy show more or less characteristic abnormalities, but they are not specific for any one type within this group. The only exception to this is myotonic dystrophy, in which the combination of histologic changes on muscle biopsy of ring fibers, sarcoplasmic masses, internalized nuclei in chains and rounding of fibers is characteristic, and in which associated abnormalities of cataracts, frontal baldness and sterility (with testicular atrophy in males) is unique.

In the group of myopathies, serum enzymes (SGOT, SGPT, creatine phosphokinase and lactic dehydrogenase) and 24 hour urine collections for creatine and creatinine are useful in supporting the diagnosis of muscle disease. Though particularly high values of enzymes are often encountered in myositis, and creatine phosphokinase may reach very high levels in pseudohypertrophic muscular dystrophy, these abnormalities are not diagnostic of any particular type of myopathy.

Muscle Biopsy

For diseases in any of the diagnostic categories, electromyography and muscle biopsy are usually indicated. Electromyography is discussed elsewhere

in this symposium. A few comments regarding the performance of the muscle biopsy are appropriate at this time.

Selection of the biopsy site should be made after a complete examination. The major goals are to get an adequate sampling of muscle, and to biopsy muscle which is not so wasted or diseased as to show only end-stage changes of little diagnostic value. For these reasons, we select two separate muscles, usually one proximal and one distal, demonstrating different degrees of involvement but not marked atrophy. The surgeon performing the biopsy should be well briefed regarding the minimum adequate size of tissue excised, which is approximately 2.5 cm by 1 cm by 1 cm in an adult patient. He must be informed that the tissue is to be excised as quickly as possible with only local procaine infiltration of the skin, or general anesthesia for children, and with a minimum of manipulation and clamping. The muscle should be immediately wrapped in saline soaked gauze and dispatched to the laboratory for processing. Delay in processing the biopsy for histological and histochemical study or failure to establish liaison between the laboratory and surgeon prior to the biopsy may make adequate evaluation impossible. Biopsies for electronmicroscopic examination require even more meticulous scheduling and handling.

The information gained by muscle biopsy is often sufficient to establish the diagnosis of neurogenic as opposed to myopathic disease; it is less frequently sufficient, at the present stage of development, to specify the precise etiology or subcategory to which the case belongs. The exceptions, in addition to those already mentioned whose diagnosis depends on specific biopsy findings, also include specific infectious disorders of nerve or muscle such as trichinosis or leprosy. A normal muscle biopsy is not to be interpreted as indicating absence of neuromuscular disease. It simply reflects absence of morphologic changes and cannot nullify clinically demonstrable impairments of muscle and nerve function.

Laboratory Studies

The laboratory studies most useful in evaluating neuromuscular diseases can be summarized as follows:

Routine studies

CBC, urinalysis, sedimentation rate, chest X-ray, serum proteins and electrophoresis, glucose, serum electrolytes (especially calcium and potassium)

Metabolic studies for disorders of muscle function or associated inflammatory or autoimmune diseases

Serum enzymes (SGOT, SGPT, CPK, LDH) LE preparations, latex fixation, C-reactive protein, liver function tests; liver biopsy, skin tests (PPD, sarcoid)

Urine for 24 hour totals of creatine and creatinine, urinary coproporphyrins, myoglobin

Endocrine studies

PBI, BMR, RAI
Glucose tolerance test
Provocative tests to evaluate end-organ response
Urinary 17-Ketosteroids
Testicular biopsy

Studies for associated neoplasm

Gastrointestinal X-rays including upper GI and colon series
Intravenous pyclogram
Bone marrow aspiration
Lymph node biopsy

Neurophysiological and pharmacological studies

Electromyography
Conduction velocity
Tensilon test

Muscle Biopsy

Histology
Histochemistry
Biochemistry
Electronmicroscopy

SUMMARY

The evaluation of neuromuscular syndromes may seem at first extremely complex because of the many systemic diseases which may present as such syndromes, and because of combinations of inconsistent terminology and apparently arbitrary separation of closely related syndromes. What is attempted here is an approach based on broad, clearly defined clinical syndromes which can be established at the bedside and subsequent to which appropriate laboratory examinations may be undertaken for further diagnosis. Though most cases can be accurately diagnosed, definite limitations of both the examination and laboratory studies exist. Stress has been placed on the need to accept these limitations until more detailed classification becomes possible, based on increased experience with intensive investigation of a wide variety of neuromuscular disorders.

Observations on Some Methods of Clinical Neurophysiology

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Clinical neurophysiology has two distinct but closely related functions, one investigative and the other diagnostic. There is methodological overlap of these two functions to the extent that both depend on the development and application of the same experimental techniques. These consist of quantitative electrophysiologic and psychophysical measurements performed for the purpose of investigating the functional status of the human nervous system. The difference is largely one of orientation. Research in this area is directed towards an understanding of mechanisms upon which human behavior rests, while diagnostic efforts are bent towards the recognition of departures from carefully established norms. Although much of the increase in diagnostic power, realized and anticipated, derives from experimental work, it is not true to say that the connections between the two aspects of this laboratory science are all in one direction. Just as behavioral sciences draw effectively from clinical observations on patients with disordered nervous systems so has experimental neurophysiology profited from the recognition and characterization of abnormal function encountered in various disease states.

There are several ways of classifying the activities included within this laboratory specialty of neurology. There is the traditional subdivision by procedure, i.e. electroencephalography, electroretinography, electromyography, etc. Table I shows the considerable overlap between these subdivisions on the basis of physiological focus of investigation and the nature of the signals to be recorded. All of the procedures in this partial list are concerned to some extent with the analysis of spontaneous activity as well as with the activity evoked by controlled stimulation.

Some Problems in Analysis of Bioelectric Data

The conventional instrumentation and techniques used for recording variations of potential differences across regions of the scalp are discussed elsewhere in this monograph in the article on electroencephalography. The bioelectric signals which are usually recorded as functions of time have attributes in common with data arising from other physical processes. For this reason it is possible to supplement the essentially qualitative pattern-recognition procedures employed by the diagnostic reader with analytical methods used in numerous other branches of science. For meaningful application, these tech-

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TABLE I

A partial list of procedures used in clinical neurophysiology showing overlap in signal characteristics and in physiological purpose. The ranges commonly used in routine diagnostic procedures are indicated in each case. Figures in parentheses indicate the extreme ranges for recording phenomena of interest

Procedural Designation	Physiological Focus of Investigation	Signal Characteristics	
		Amplitude Range	Band Width
		(Volts)	(Hz)*
Electroencephalography	Sensory function	$10^{-5} - 10^{-3}$	1 - 70
Electrocorticography	Motor function	$(10^{-7} - 10^{-1})$	(DC - 10,000)
Depth Recording	Cerebral mechanisms		
Electrooculography	Vestibular function	$10^{-5} - 10^{-3}$	0.1 - 70
	Visual function	$(10^{-5} - 10^{-2})$	(DC - 100)
	Oculomotor function		
	Brainstem and cerebral mechanisms		
Electroretinography	Visual function	$10^{-5} - 10^{-3}$	0.1 - 70
		$(10^{-7} - 10^{-2})$	(DC - 2,000)
Electromyography	Motor function	$10^{-5} - 10^{-2}$	5 - 5,000
	Sensory function	$(10^{-6} - 10^{-1})$	(DC - 10,000)

* According to universal convention, Frequency is now measured in Hertz (Hz) rather than in the old unit of "cycles per second." Thus 1 Hz is identical with 1 cps, 1 KHz = 1000 Hz with 1 Ke and so forth.

niques impose certain constraints on the signals, but once the conditions are satisfied it is of no mathematical consequence whether the signals "belong" to the oceanographer, the astrophysicist, the communications engineer or the electroencephalographer.

It must be immediately pointed out that none of these methods of analysis, either analog or digital* will add information† to that already present in the conventional recording. On the other hand, the data contained in an EEG tracing is in such a form that much of it is unavailable to the reader. Even more troublesome is the fact that this mode of presentation almost always leads the reader to erroneous assumptions both about the nature of the signal and the underlying physical process. Consider, for example, the waveform at the bottom of Figure 1A. Assume that the sample is derived from a longer segment of record which contains identical patterns. The record would then be said to *signify* or *contain* one-second bursts of nine-and-a-half-cycle "activity" with maximum amplitude of (say) 50 microvolts. This description is, of course, quite correct as long as it is understood to apply only to the pattern of squiggly lines on the paper. In this case, however, the pattern was actually derived from

* Analog processes or methods or functions are continuously variable in contrast to digital which vary in discrete steps.

† Information used here in the technical sense.

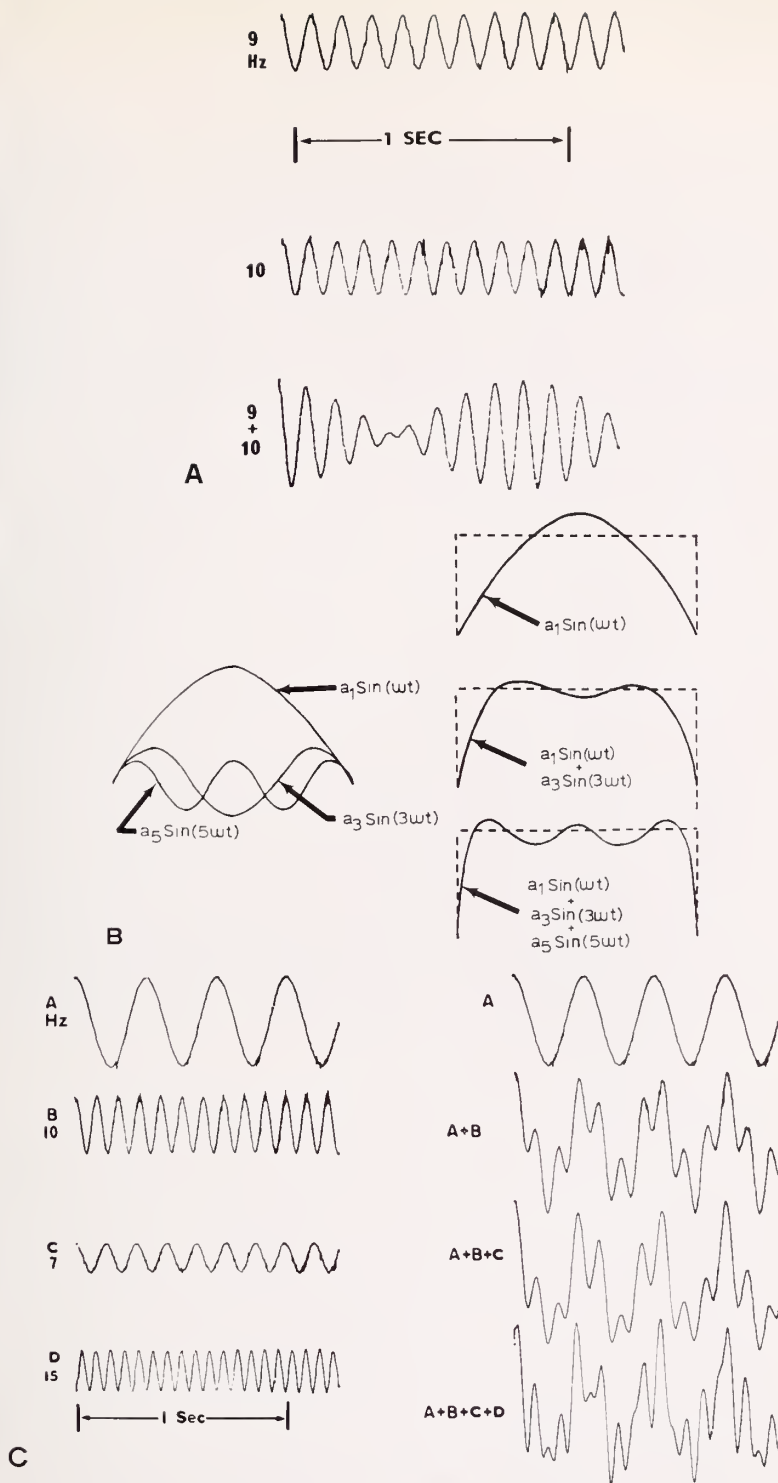


FIG. 1. A. Addition of sinusoidal waveforms. B. Synthesis of a complex waveform by stepwise addition of the first two odd harmonics to a 1 Hz fundamental. C. A further example of synthesis showing the elementary component waveforms, each of different frequency which are contained in the sum.

the simple addition of "activity" from two generators each contributing a 25 microvolt output to the recording system, one oscillating at a frequency of nine cycles per second and the other at a frequency of ten cycles per second. A record containing a similarly repeated pattern 0.5 seconds of which is shown in (lower right) Figure 1B, might be reported in part as "six-cycle-per-second activity superimposed upon high amplitude one-cycle-per-second slow waves." The remaining parts of the figure show how the linear combination of three frequencies, none of which is 6 Hz, can result in the observed waveform. The more complex waveform shown in Figure 1C along with its component signals, that is, the signals it "contains," shows how difficult the task of deducing spectral content from the EEG record can become.

Fortunately, the clinical interpretation of a record is rarely troubled by these difficulties which, as can be seen from the above illustrations range from formal, semantic errors to fundamental technical and conceptual weaknesses. Attention has been called to these difficulties many times during the past three decades, but we will review them here for two reasons. The first is to indicate to the critical reader that the material presented in some articles in this monograph laboratory section has been extensively simplified and, therefore, cannot provide completely satisfactory models of modern laboratory philosophy or practice. The second reason for reviewing some less well-known principles and techniques is to assure the reader who is interested and concerned about the present shortcomings of the field of clinical investigation that it is by no means stationary. There is no guarantee that an improvement in accuracy and depth of analysis will ever provide a corresponding increase in diagnostic accuracy. Certainly none of the techniques of signal analysis has yet made many significant contributions to the clinical value of the EEG, but this is principally because many of the original applications have terminated with a quick and dirty first look at the problem. It is hardly likely, however, that sustained systematic effort in this direction will fail to yield some significant advances.

Other Useful Methods of Signal Analysis

Correlation

There are under consideration many schemes for classifying natural phenomena according to the similarity of their attributes, but the general problem is too difficult to outline adequately in this article. (See Ornstein, L., *J. Mt. Sinai Hospital* 32: 437, 1965.) One of the less powerful methods which has received some attention in electrophysiology because it is simple and inexpensive is the computation of correlation between two signals under a shift in time. A signal may be correlated with a replica of itself shifted in time (autocorrelation) or with another, different signal also as a function of time delay (cross-correlation. Consider, as an example, the tracings shown in Figure 2, all identical except for a progressive delay in the writeout established by an appropriate displacement of the oscillograph pens. Notice that for zero time shift

the waveforms are perfectly correlated. This is to be expected, of course, since they are identical. Note also that as the delays increase to nearly 100 milliseconds the correlation first diminishes and then rises again towards a new maximum as suggested by the realignment of peaks and troughs in the waveform. If we continue to shift the trace relative to itself in this way there will be a waxing and waning of correspondence which repeats at intervals determined by periodicities in the original waveform.

A graphic computation of an autocorrelation is illustrated in Figure 3. Here the signal is a rectangular wave. Again we observe that the correlation is maxi-

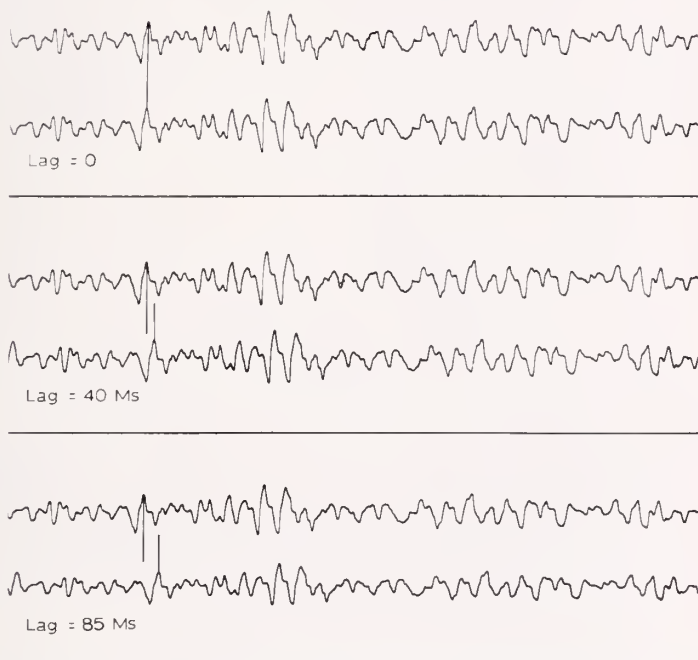


FIG. 2. Comparison of EEG waveform with itself at three different delays. The lower trace in each pair has been shifted by the amount indicated in the figure.

imum (equal to $+1$)* when no delay is introduced. If we now shift the signal relative to itself by an amount equal to one lag unit, the area of overlap is reduced. And so it is with each successive delay until the lag equals the pulse duration. At this time, and for all successive delays, the common area is zero. For each lag we take the common area as the measure of correlation and in this way arrive at the linearly decreasing function shown in the bottom left-hand corner of the figure. Using arithmetic methods analogous to this graphic computation we can determine the autocorrelation of the waveform in Figure

* If one of the two waveforms to be correlated was the reflection of the other about the time axis (i.e. upside-down), the correlation would be maximum here also but equal in value to minus one.

1C. This is recorded in Figure 4 in which the magnitude of correlation is plotted as a function of the lag (or shift). Two further examples are given in Figure 5.

It is clear that with this mode of analysis we can detect some periodicities that may be masked in the conventional voltage versus time recording. From the crosscorrelation of two different signals we can make explicit some information about common periodicities. Also since the maximum correlation between two signals may occur at some lag other than zero, we can derive from the crosscorrelogram some explicit information about phase relations. This can be useful in comparing EEG rhythms recorded from symmetrical regions of the scalp and also in determining the sequence of activity arising from deep

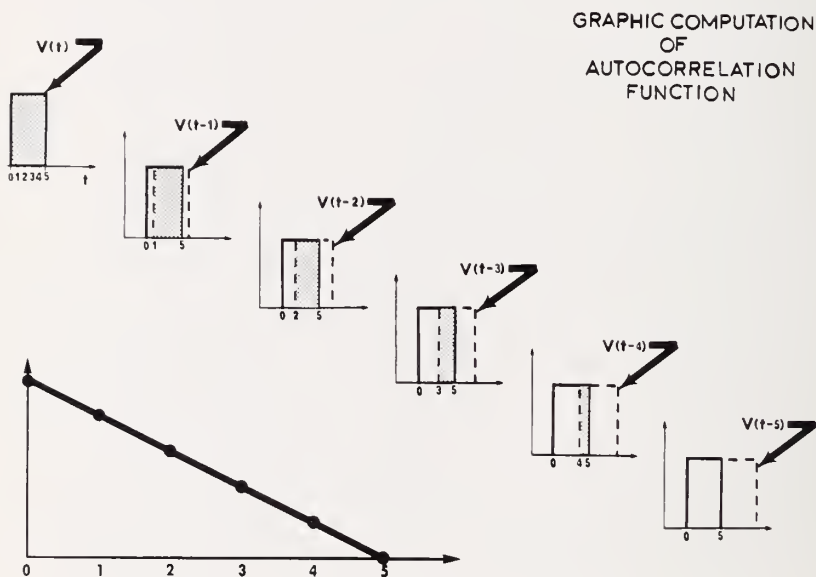


FIG. 3. Graphic computation of autocorrelation.

structures in the brain. There are many limitations to the power of correlation techniques, not all of which can be discussed here. Suffice it to say that correlation cannot display in a convenient form all of the potentially useful information contained in the signal. For example, the resolution of a waveform into its constituent frequency components or the comparison of spectral content of different signals requires other methods of analysis.

Spectral Analysis

The most familiar form of frequency analysis in electrophysiology is that derived by splitting the signal into a number of narrow frequency bands by filtering and, usually, adding the voltage in each band over a fixed period of time. In this way one can view a display of amplitudes over intervals in the frequency domain and, for example, determine that the signal in Figure 1A "contains" frequencies of 9 and 10 Hz.

FIG. 4. Autocorrelation of EEG showing major periodicity.

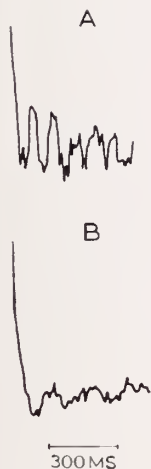
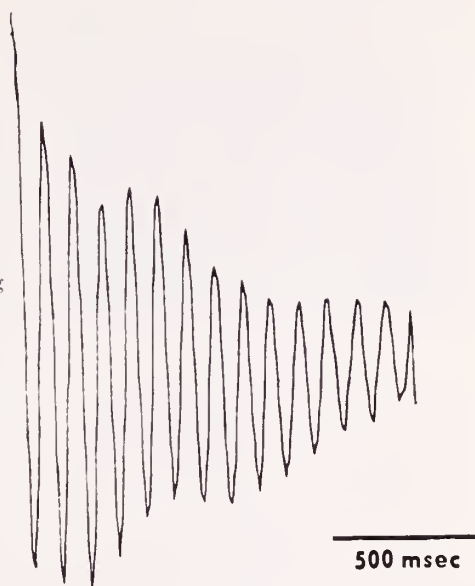


FIG. 5. Additional examples of autocorrelograms. Upper trace derived from parietal-occipital recording made on a normal male adolescent. Lower trace from same electrode pair in decerebrate adult.

This method of frequency resolution has also been applied sporadically to electromyography but so far not to any profound purpose. It has also led to a certain amount of confusion among clinical electromyographers concerning the relation between pitch of the signals observed during the recording and "spectral content" of the signal. For example, the celebrated "dive-bomber" sounds heard in recordings from myotonic muscle (Fig. 6) are related to the repetition frequency of the component spikes in the discharge. As the frequency

of discharge diminishes, the pitch drops. A spectral analysis will, of course, show corresponding changes in the distribution of component frequencies monitored, but the changes in *content* of the complex signal are themselves very complex. This is equally true for the acoustic clues used to detect changes in duration of unit potentials. The shorter the unit, of course, the higher the pitch but again the spectrum of such myopathic potentials changes in other ways than by simple shift in amplitudes towards a single higher frequency (Fig. 7).

Many other methods of obtaining approximate spectral information about signals such as those encountered in clinical neurophysiology have received some attention, particularly those based on easily derived measurements of the variation and "wiggleness" of the signal. These will not be further discussed. The spectral density of a signal (Fig. 8) presents, in perhaps the clearest manner, the distribution of energy over a range of frequencies. The abscissa labelled "lag number" indicates the derivation of this plot from an intermediate computation of the autocorrelation function.

Implied in the foregoing discussion is the fact that operations on waveforms like the EEG, designed to make evident certain aspects of the signal, cost something. In general, the sharper the focus of attention, the higher the price in terms of the total amount of information available for analysis. The trick is to characterize the signal in ways that will yield the most important data for the physiological problem at hand. There is no "absolute best" method. The most valuable technique depends on the nature of the system studied and the purpose of the investigation. In most cases more than one method of analysis will be required.

Sensory Physiology and "Small Signal" Analysis

The electrophysiologic investigation of sensory function in humans requires special consideration. This problem, more than any other, unites the several subdivisions of Clinical Neurophysiology. For example, it is clear that measurements of the observable electrical effects of optical stimulation on responsive elements of the nervous system is more conveniently done in a single laboratory, with requisite experience and equipment for measuring the peripheral as well as the central responses. An electroretinogram such as the one shown in Figure 9 may be of limited value unless the study is extended to observation on generators further along in the visual pathways. This is also true for somatosensory and auditory function.

All of the analytical methods discussed thus far are, of course, applicable to the study of sensory function. Additional techniques are sometimes required because, in general, the signals derived in response to stimulation are small compared to the background activity and small even with respect to the noise in the recording system. Again there are several ways to approach the problem of small signal analysis. Those most frequently used are directed towards enhancing the signal by discriminating against background noise. To date the most effective technique of this kind is *average response* computation. In its simplest application "averaging" depends on the fact that all elements in the

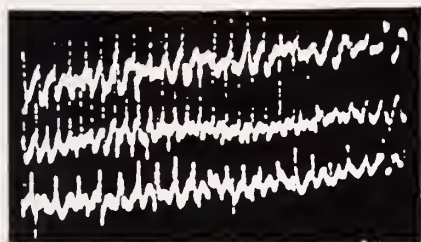


FIG. 6. High frequency discharge recorded from myotonic muscle. Time calibration—50 milliseconds.

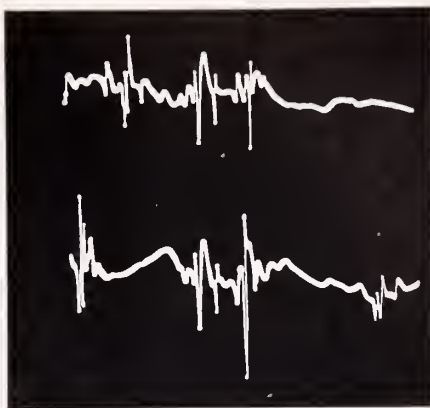


FIG. 7. Potentials recorded from a patient with clinically recognized myopathy during slight voluntary effort. Time calibration—5.0 milliseconds.

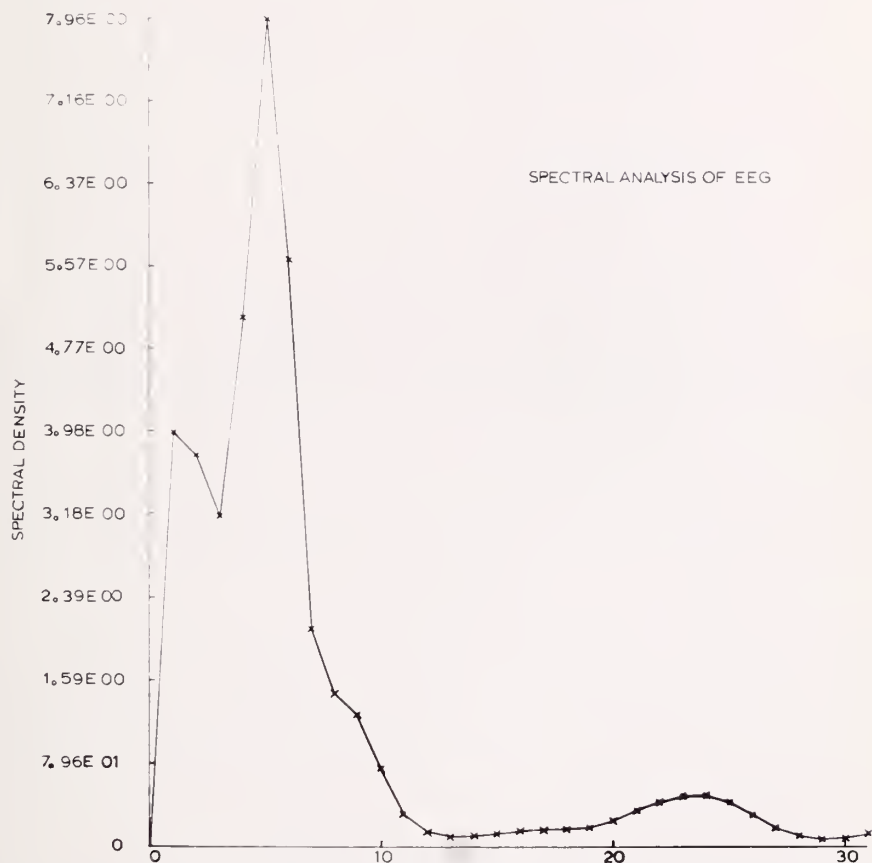


FIG. 8. Spectral density computed from an EEG (right occipital to right posterior temporal derivation) of normal young adult. Abscissa is marked-off in lag numbers, each lag corresponding to 2.5 Hz. Notice the truncation of the first peak in the waveform which is probably an artifact resulting from the coarse grain employed in the analysis.

complex waveform occurring at fixed intervals after some event (e.g. a stimulus) can be distinguished from those elements which vary randomly with respect to that event, by simple, repetitive addition of waveforms over some interval of time *always beginning with the stimulus*. The resultant sum is proportional to the average sample, hence its designation as "average response."

The efficiency of this technique is shown in Figure 10. In the top trace we show a prominent waveform within which is "buried" a small signal (in this case a rectangular wave). This signal *always* occurs at the same time interval after a signal which serves to trigger the trace. On the other hand, the prominent components of the waveform which are not of interest to us, are not

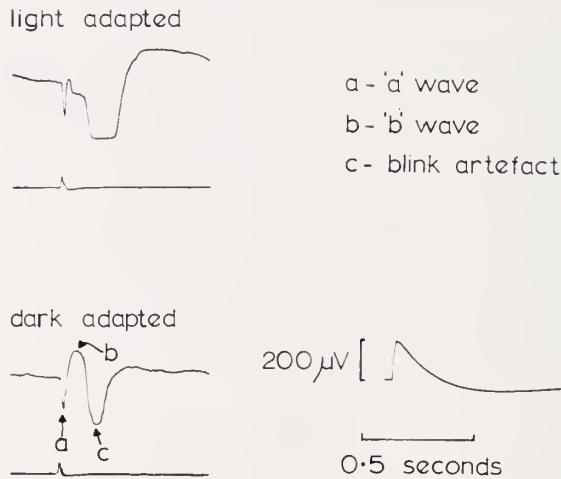


FIG. 9. Normal electroretinogram. An upward deflection indicates an increase in relative positivity of the cornea with respect to the reference electrode. Tracing was made from a patient with familial degenerative disease of the nervous system in whom retinitis pigmentosa had been suspected.

time-locked to the trigger signal and so will vary in position from sample to sample. By adding a large number of such samples, we can expect that the time-locked rectangular wave (signal) will get larger, because no matter how small the signal is in each sample, it will make that same small contribution each time to the sum of the samples. At the same time, the "undesired" background will diminish because of cancellations in the sum. The resulting signal-to-noise improvement, as a function of the number of samples added, is shown in the remaining traces in Figure 10. Application of this principle to sensory-evoked potentials is technically straightforward, but reasonable sophistication and great care is required in order to avoid the serious methodologic difficulties with which the procedure is fraught. (*Ann. New York Acad. Sc.* 112: 160 (May) 1964).

Some illustrations of sensory evoked potentials are given in Figures 11, 12, 13 and 14. One point of clinical importance that should be stressed here is the need for thoughtful restraint both on the part of the physician requesting infor-

mation and the physician who, with the aid of laboratory instruments, attempts to provide it. The need for restraint relates to the premature identification of electrical activity with psychic functions. While there is some evidence and much hope that analysis of bioelectric data may in the future yield objective evidence about behavior, particularly sensory behavior, it does not yet do so reliably. For the present, it is more appropriate to ask and answer clinical laboratory questions of the form, "Does acoustic (or optic or

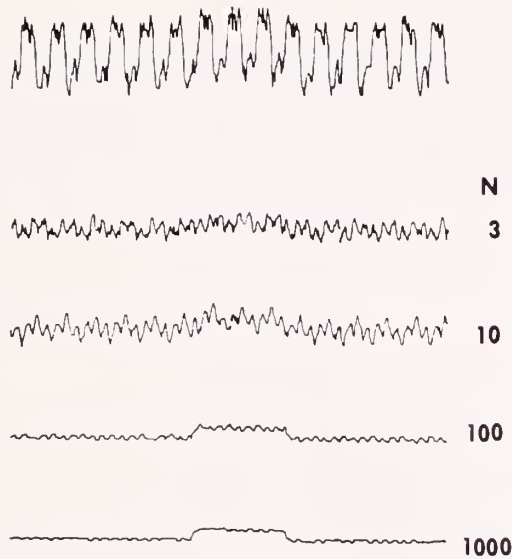


FIG. 10. Illustrates average response computation. A single sample containing a rectangular wave signal is shown in the top trace. Note the improvement of signal-to-noise ratio as a function of the number of samples added. Display amplitude has been reduced by an amount approximately proportional to the number of samples in each trace.

electrocutaneous) stimulation produce a normal electrical response?" rather than, "Does the patient hear (or see or feel)?"

SUMMARY

It should be clear from this survey that we have not yet exhausted all possibilities for providing diagnostic assistance to the clinical neurologist. In fact the state of the art has already taken us beyond the reliability and power of some of the techniques that are outlined elsewhere in this monograph.

Only a small fraction of the advances in clinical electrodiagnostic procedures can be attributed to improved instrumentation. It is increasing knowledge and control of the equipment and better understanding of physiological principles that has, to cite one example, made serial measurements of conduction velocities almost as accurate a procedure as most clinicians erroneously

believe it to be. There is, of course, still a difference between what diagnostic assistance can be offered by rigorous technique and what is actually achieved after the sacrifice of information by approximate procedures. In sum, diagnostic clinical neurophysiology is of some definite but limited assistance to a good neurologist. It rarely offers him new information. For example consider that more than one-third of patients known to have disorders of the lower motor neuron have no diagnostic abnormality revealed in the electromyographic examination, and more than 25 percent of patients with known convulsive disorders have normal EEG's.

At the present time, none of these electrophysiological subspecialties including EEG or EMG is a substitute for competent clinical neurological opinion. The most interesting and potentially productive uses of the diagnostic testing are, by carefully observing and analyzing the physiological manifestations of neural dysfunction, to follow the patterned changes in the course of disease processes and to learn something more about how the normal nervous system works.

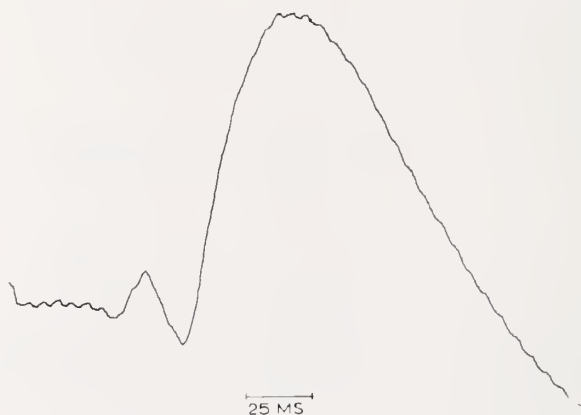


FIG. 11. Visual potential recorded from the vicinity of the lateral geniculate body in a decerebrate patient.

FIG. 12. Visual evoked potentials showing variation in waveform corresponding to changes in state of the nervous system. Trace *a* and its continuation, trace *b*, were derived from the EEG of a sleeping subject by the addition of 200 samples, each immediately following a brief, intense photic stimulus. Traces *a'* and *b'* are the corresponding averages obtained under identical recording and stimulating conditions, except that the subject was awake. Each trace is 0.5 seconds in duration. The raw EEG record showed no evident response to any of the single light flashes.

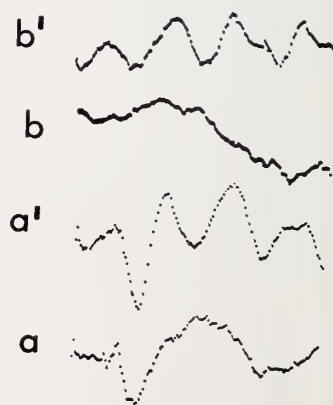




FIG. 13. Scalp potentials recorded by adding EEG samples obtained in the 250 milliseconds following acoustic stimulation with 1 KHz sine wave rising to 50 db sensation level in 10 milliseconds. Upper traces: Vertex to Right Occipital; Lower traces: Vertex to Left Occipital. Number of response samples: 600 in the left-hand traces and 800 in the right.

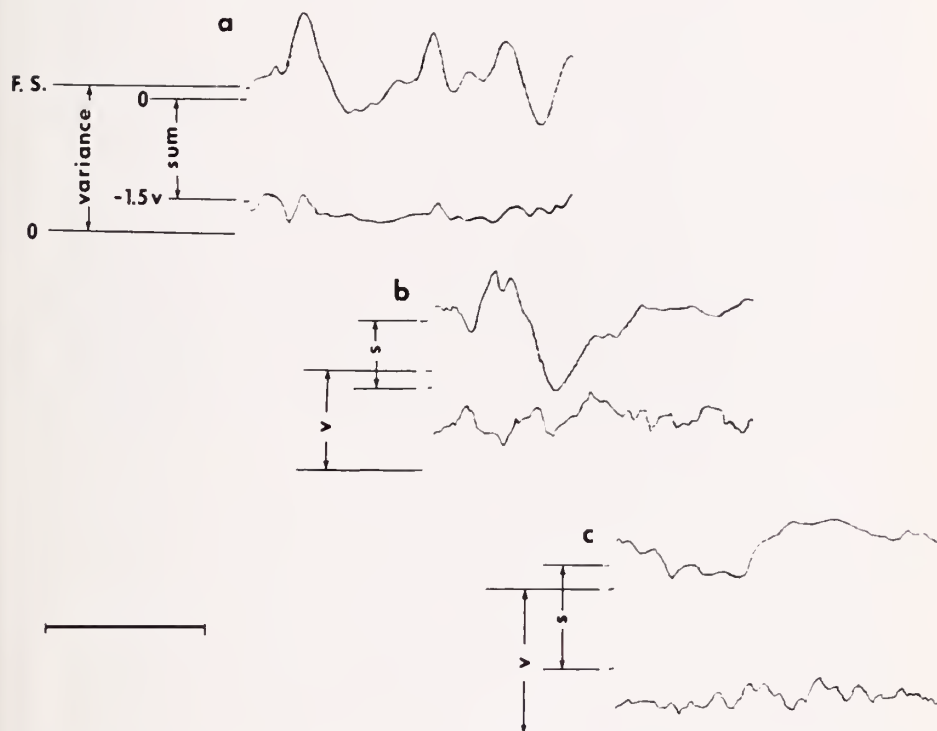


FIG. 14. *Upper traces*, Average response to 25 brief, intense photic stimuli. *Lower traces*, Variance of evoked potential computed from the set of values at each point of response waveform.

a) Control b) After 500 mg Metrazol administered intravenously over a ten minute period c) Same patient following intravenous injection of 350 mg sodium amytal. In each case the variance provides information which is not contained in the summed (average) response and, in fact, assists in its interpretation.

These computations were performed on-line using a Bio-Data Corp. Model 204 Variance Computer. Zero and calibration markers for both the average response and the variance are provided at the left margin of the figures. Time calibration 250 msec.

Herniation and Strangulated Incarceration of Small Intestines in the Foramen of Morgagni

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Herniation through the foramen of Morgagni is widely regarded as a rare and benign lesion. This assumption may on occasion prove dangerous as illustrated in the case presented here.

A 23 year old male was omitted to City Hospital Center at Elmhurst, January 3, 1965 with a chief complaint of right upper quadrant pain and vomiting of 48 hour duration. In excellent health until the onset of these symptoms, the patient had practiced professional boxing for several years but had stopped this activity for nonmedical reasons two years prior to hospital admission. The patient occasionally drank alcoholic beverages. He was recovering from a vigorous New Year's celebration when the pain started.

Physical examination revealed a moderately obese male who was dehydrated, apprehensive, and complaining of abdominal pain. Clinical examination disclosed temperature, 99.6 F., pulse, 90, blood pressure, 130/100, skin dry and warm, no jaundice or cyanosis. There were decreased breath sounds over the right lower chest, and no record of peristalsis in this area. The abdomen was moderately distended, generally tender, and very tender over the right upper quadrant, no rebound and increased peristalsis. Laboratory studies disclosed the following values: White blood count 12,700, hemoglobin, 14 gm/100 cc, blood urea nitrogen, 10 mg/100 cc, blood sugar level, 120 mg/100 cc, carbon dioxide, 24 mEq/liter, chlorides, 104 mEq/liter, potassium, 3.4 mEq/liter, sodium, 138 mEq/liter. Chest x-ray revealed multiple air-filled loops of small bowel and absence of air in the colon. Contrast study was unrevealing except for a reversed duodenal sweep. The patient's general condition deteriorated despite rehydration and intubation, and pain became more severe and persistent. A clinical diagnosis of right diaphragmatic hernia and small bowel obstruction with impending strangulation was made, and five hours after admission the patient underwent surgery. A standard posterolateral thoracotomy was performed. Findings revealed a baseball-sized hernia originating from 4 in across a retrosternal defect, containing 4 feet of small bowel, transverse colon, omentum and the left lobe of the liver. The thick fibrous sac was firmly adherent to the contained organs. A laceration at the apex of the sac allowed a loop of jejunum to be in contact with the lung. No adhesions were found, indicating recent development. The herniated bowel was distended and edematous but

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viable. The defect was enclosed about two-thirds by a thickened rim of diaphragm. In the anterior one-third, the sac arose directly from the chest wall at the level of a normal diaphragmatic insertion.

The hernial content was dissected and reduced and the diaphragm was opened wide along its lateral attachment. Medial sliding of this mobilized portion allowed a relaxed closure of the defect. Suture of the flap to the fibrous base of the sac secured a solid costophrenic attachment.

The patient had an uneventful postoperative course and was discharged on the eighth postoperative day. At follow-up, he was found asymptomatic and chest x-ray showed a normal diaphragmatic contour. A gastrointestinal series will be performed.

COMMENT

Hernia through the hiatus of Morgagni is the rarest of all diaphragmatic hernias (1, 2). Its incidence increases with advancing age, and in order of frequency, the organs involved are the omentum, colon, stomach, liver and small bowel. There is general agreement that the symptoms are mild and significant complications rare or even absent in some series (3). Acute mechanical obstruction of the small bowel must be very rare, and we have found only one reported case (4). More often the complications leading to surgery have been intermittent obstruction of the pylorus or colon (5). The indications for surgery have been limited to the complicated case and to diagnosis of intrathoracic masses. The case presented here illustrates that bowel herniated through a retrosternal defect is subject to the well known complications of any other hernia, i.e. mechanical obstruction and strangulation. An older patient may not have tolerated the rapid deterioration observed in this patient as well as he did. A case can be made for elective surgery in the individual patient who is asymptomatic, if the presence of bowel in the hernia can be demonstrated.

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UNUSUAL PROBLEMS IN SURGERY

LEWIS BURROWS, M.D. AND JACK RUDICK, M.D.

CASE NO. 3

Primary Mesenteric Venous Thrombosis

In contradistinction to mesenteric arterial occlusion, which is usually embolic, mesenteric venous occlusion is always thrombotic in nature (1). Since the differentiation in 1935 by Donaldson and Stout (2) of mesenteric venous thrombosis as an entity distinct from arterial thrombosis, 37 patients with primary mesenteric venous thrombosis have been documented in the literature. A case of primary mesenteric venous thrombosis was recently encountered in the surgical service of Elmhurst Hospital which illustrates many interesting features in etiology, mode of presentation, diagnosis and operative findings.

CASE REPORT. An 81 year old white female was admitted to the surgical service of Elmhurst Hospital July 24, 1966 complaining of vague abdominal pain and vomiting of one week duration. The pain was initially colicky and diffusely located in the lower abdomen but became more severe and constant on the day prior to admission. The patient vomited several times daily; the vomitus containing dark gastric content. She was constipated for two days and passed no fresh or altered blood per rectum.

Appendectomy had been performed 30 years previously, and the patient suffered a mild cerebrovascular accident with residual slight right hemiparesis seven years prior to

admission. She had also been treated for mild diabetes which was adequately controlled on diet alone.

PHYSICAL EXAMINATION. Physical examination on admission revealed a frail, thin woman in no acute distress. The pulse rate was 80 per minute, blood pressure 140/80 mm Hg, and temperature 99.8 F. A scar from the previous appendectomy was present, as were easily reducible bilateral inguinal hernias; no tenderness was present over the inguinal rings. There was initially tenderness in the lower abdomen, shifting to the upper abdomen, and later becoming diffuse over the whole abdomen. Bowel sounds were present and not of the obstructive type. Rectal examination failed to reveal any abnormality. There was no clinical evidence of intestinal obstruction. Apart from the slight right-sided residual hemiparesis the rest of the physical examination was essentially negative. No cardiac arrhythmias were noted. Leukocyte count was 17,800, hemoglobin concentration was 15.8 gm/100 cc, and the hematocrit level 51%. Blood sugar was within normal limits. Urinalysis was essentially normal. Plain film of the abdomen revealed gas in the large bowel and an abnormally large amount of gas in the stomach, suggestive of volvulus of the stomach (Fig 1).

HOSPITAL COURSE. A conservative regime was instituted, comprising nasogastric suction and intravenous fluid therapy. There was essentially no alteration of the clinical picture. Barium examination of the stomach failed to confirm a diagnosis of the volvulus, and a small bowel series was continued. The barium passed freely into the proximal 3 to 4 feet of jejunum where a 1 to 2 foot segment of narrowing with rigid appearance of the loop was noted (Fig 2). The barium nevertheless passed freely through that segment and there was delay of passage of barium at the ileocecal region with a filling defect in the cecum. Due to the filling defect

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Case No. 3, Fig. 1. Plain radiograph of abdomen which shows gas in large bowel and abnormally large amount of gas in stomach, suggestive of volvulus of the stomach.

Case No. 3, Fig. 2. Barium examination of stomach and small bowel. A 1 to 2 foot narrowed segment of jejunum with rigid appearance of this loop is noted about 3 to 4 feet from the duodenojejunal flexure. The barium passed freely through this segment but there was delay of passage of barium at the ileocecal region.

Case No. 3, Fig. 3. Photograph of operative specimen. Scattered hemorrhagic areas and patchy gangrene is noted in jejunum approximately 4 feet from duodenojejunal flexure. The mesentery of this segment is gangrenous but arterial pulsation was noted both in superior mesenteric artery and in smaller vessels of the vascular arcade.

and hold-up of barium at the ileocecal region a diagnosis of intestinal obstruction was made, probably secondary to adhesions from the previous appendectomy.

The patient subsequently developed increasing lower abdominal distention and

tenderness. The additional feature of hypoactive bowel sounds now suggested an acute intestinal obstruction requiring immediate surgery.

OPERATIVE FINDINGS. The peritoneal cavity contained over 2,000 ml hemorrhagic fluid.

There was no evidence of internal herniation, and no adhesions were noted. A one foot length of small bowel approximately four feet from the duodenojejunal flexure was the seat of patchy gangrene with scattered hemorrhagic areas (Fig 3). Approximately one foot on either side of the segment was markedly congested and edematous. The mesentery of the segment was gangrenous but arterial pulsation was noted in the mesentery both in the superior mesenteric artery and in the smaller vessels of the vascular arcade. Approximately three feet of the small bowel and its mesentery was resected, intestinal continuity being restored by end-to-end anastomosis. The postoperative course was uneventful, postoperative medication including antibiotics and anticoagulants, heparin and Coumadin.

Pathological examination confirmed the presence of severe acute inflammation, mucosal ulceration and edema, congestion and gangrenous changes in the resected specimen. Several of the veins examined contained thrombi. No thrombi were noted in the arteries which did show mild to moderate arteriosclerosis.

DISCUSSION. Although mesenteric vascular occlusion was first described by Antonio Benivieni in the latter part of the 15th century, this condition did not receive recognition by the medical profession until the 19th century. In recent years an increasing number of series have been reported but there has been a general tendency to consider arterial, venous and mixed types as one group. Since the separation of mesenteric venous thrombosis as a distinct entity by Donaldson and Stout (2) there has been an increasing recognition of this condition. Extensive reviews of the world literature have been discussed by Berry and Bougas (3) and by Naitove et al (4) who have further subdivided mesenteric venous thrombosis into a primary and secondary entity.

Although the precise etiology of

mesenteric venous thrombosis is still unclear, several predisposing factors have been described. These include factors generally accepted as predisposing to thrombosis; retardation of blood flow, alterations in the composition of the circulating blood, and damage to the vessel wall. Mesenteric venous thrombosis has been reported following non-penetrating injuries of the abdomen (5, 6) and abdominal surgery (7, 8), especially splenectomy for congenital hemolytic anemia (9). It has been suggested (10) that following trauma to the intestine, toxins were present in the mesenteric venous blood which in small amounts increased the tendency to thrombosis and in large amounts decreased this tendency, but this has never been substantiated. However, McCune et al (6), comparing mesenteric and peripheral venous blood, found a differential increase in the platelet count in mesenteric venous blood, which they postulated would not affect normal vessels but would adhere to the wall of a vessel in the presence of intimal damage.

It is convenient to consider these factors in three groups (a) Mechanical venous obstruction: portal venous obstruction; pressure from tumors; adhesions; volvulus; and reduction of an incarcerated hernia; (b) Infective conditions: appendicitis; pelvic abscess; and peritonitis; (c) Trauma of any sort to the mesenteric veins; (d) Hematogenous conditions generally predisposing to thrombus formation: splenic anemia; polycythemia vera. Although other thromboembolic manifestations, e.g. thrombophlebitis, cerebrovascular accidents, have been re-

ported in patients with mesenteric thrombosis, conditions such as myocardial infarction, rheumatic heart disease, and auricular fibrillation are usually associated with mesenteric arterial occlusion.

The precipitating factors in this case can only be speculative. The bilateral inguinal hernias reduced spontaneously and were so small that they could not be held responsible. The patient did undergo surgery (appendectomy) 30 years previously, but there were no intraperitoneal adhesions to produce mechanical occlusion. The previous right hemiplegia with slight residual hemiparesis, arteriosclerotic heart disease and mild, easily controllable diabetes may have provided a milieu for the onset of the thrombosis, but could hardly be regarded as precipitating factors in this case which must be considered as one of primary mesenteric venous thrombosis.

The duration of symptoms in this

Venous Occlusion

Slow onset
Colicky pain that increases in severity as time passes
Hematemesis and melena appears early due to intestinal congestion
Minimal leukocytosis

Normal or slightly decreased blood pressure

patient exemplifies the dictum that mesenteric venous thrombosis has an insidious onset and is a slowly progressing condition. It is possible for patients with venous thrombosis of the mesentery to carry on over a period of days, as this patient did, before an operation seems indicated (11). Camp-

bell and Mears (12) have listed the symptoms and signs of mesenteric venous thrombosis.

1. Gradual onset
2. Colicky abdominal pain
3. Abdomen tender on deep palpation
4. Coffee-ground vomitus
5. Occult blood in stool
6. Absent intestinal fluid levels on roentgenogram
7. Leukocyte count not markedly elevated
8. Engorged intestinal wall may or may not be palpable
9. Temperature usually low
10. Blood on glove on rectal examination
11. Condition occurs twice as often in males than females, more frequently with advanced age.

This patient exhibited most of these clinical features. It is worth emphasizing the differences between mesenteric venous and arterial occlusion:

Arterial Occlusion

Sudden onset
Violent, excruciating abdominal pain
Melena and hematemesis appear later concomitant with the onset of gangrene
More pronounced leukocytosis, often about 40,000
Shock—patients are gray, restless and sweating

The radiologic findings provide an unusual facet of this case. Because of the original suggestion of volvulus of the stomach, a barium meal examination was performed. Since no lesion was demonstrated in the stomach, the examination was continued as a small bowel series. This case therefore rep-

resents one of the extremely few cases in which contrast studies of the small bowel have been documented preoperatively in a patient with a diagnosis of mesenteric venous occlusion. Although the narrowed rigid segment through which barium is able to flow unobstructed should alert one to the diagnosis, these features are not necessarily pathognomonic of this condition. Unlike arterial occlusion, barium studies can be carried out with minimal risk.

The pathogenesis is fairly straightforward. Venous occlusion first produces a hemorrhagic infarction which progresses to necrosis and gangrene, a process which occurs more frequently in the superior than the inferior mesenteric system. The time interval between the onset of the occlusion and the development of gangrene depends upon the site of thrombosis, gangrene occurring at an earlier stage if the thrombosis occurs in small vessels close to the bowel wall. Because of collateral circulation, thrombosis in the larger vessels may be present for several days before the viability is impaired. This factor may account for the marked variation in the duration of symptoms.

The treatment of mesenteric venous thrombosis should always be surgical. In contrast to the arterial occlusion with an overall mortality of 88.6%, venous thrombosis has a mortality rate of 30 to 35% (12, 13). However, in non-operative series, the outcome is fatal regardless of the type of occlusion (4). The line of resection should extend well beyond the infarcted segment as the thrombus may further propagate even after resection. Indeed, if there is a suspicion of extension of

thrombus postoperatively, there should be no hesitation in subjecting the patient to reexploration.

Although anticoagulant therapy is generally favored because of the recurrent nature of the disease, its use has produced conflicting results. Naitove et al (4) and Duncan et al (14) claim better results in the prevention of recurrent thrombosis with the use of anticoagulants, whereas Jenson and Smith (15) and Campbell and Mears (12) found that anticoagulant therapy did not significantly alter the outcome, adding that the additional risk incurred by the anticoagulants did not warrant its use in mesenteric venous thrombosis. Clearly, its precise role requires further evaluation. More recently, Daniel et al (16) have reported the successful treatment of mesenteric embolism with low-molecular-weight dextran. Convincing evidence of benefit from the use of low-molecular-weight dextran in dogs with experimentally induced acute mesenteric venous (17) and arterial (18) occlusion has been reported. The precise role of this substance, which has been advised in a wide variety of conditions in which tissue perfusion may be impaired, is awaited with keen interest.

SUMMARY. A case of mesenteric venous thrombosis with favorable outcome following surgery is presented, together with a review of the literature. Several aspects have been emphasized: the insidious onset, diagnostic features and the favorable results with operative management.

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CASE NO. 4

Lymphangioma of Retroperitoneum and Mesentery

Retroperitoneal and mesenteric lymphangiomas are tumors of lymphatic origin which are histologically similar to the more common cystic hygromas of the neck found in children (1). Their appearance in the retroperitoneum and leaves of the mesentery, however, represents a very uncommon circumstance. In a series of 15,000 necropsies performed at the University of Minnesota (2), there were no retroperitoneal lymphangiomas found. In a larger necropsy series (2), only two cases of these chylous cysts were found amongst 200,000 cases. A report by Behrs et al (3) from the Mayo Clinic describes only nine cases of similar tumors found at surgery from 1911 to 1947. Parsons (4), in 1936, reported 500 cases of mesenteric cysts and only ten of these were classified as lymphangiomas. Harrow (5) in 1957, reviewed 600 cases of mesenteric cysts and only 14 of these were of lymphatic origin. A report by Pack and Tabah (6) in 1954 reveals no cases of lymphangioma among 120 primary retroperitoneal tumors. We are presenting a case of retroperitoneal lymphangioma occurring in a young male treated at the surgical service at The Mount Sinai Hospital.

CASE REPORT. A 28 year old white man was admitted to Mount Sinai Hospital for the first time complaining of fever and right

lower quadrant pain. He was well until six months prior to admission when he began to note intermittent right lower quadrant aching, periumbilical pain, without any other gastrointestinal complaints. Occasionally, he observed fullness in the right lower quadrant. Ten days prior to admission, the patient began to experience low-grade fevers and three days prior to admission, following heavy exertion, the periumbilical pain became more severe, and the patient sought admission to Mount Sinai Hospital.

The review of systems was essentially negative without any other gastrointestinal or genitourinary complaints.

PHYSICAL EXAMINATION. The patient was a thin, well-developed white male. Blood pressure was 120/80; pulse rate 100 beats per minute; respirations 12; temperature 102 F. Physical examination was within normal limits except for the abdominal findings. On examination, there was tenderness and guarding with an ill-defined mass palpable in the right lower quadrant. No other masses or organs were palpable, and bowel sounds were hypoactive. No hernias were found and a rectal examination was unrevealing.

LABORATORY DATA. The hemoglobin level was 12 gm/100 cc; white blood count 16,000 with a shift to the left. Urinalysis revealed trace of albumin and 3 to 4 white cells per high power field. BUN was 23 mg/100 cc, electrolytes and liver function studies were within normal limits. A chest x-ray was normal and abdominal films revealed a mass located primarily in the right side of the abdominal cavity pressing upon the ascending colon.

An intravenous pyclogram revealed a large retroperitoneal mass which displaced the right ureter to the midline and anteriorly with a moderate degree of right sided hydronephrosis and hydroureter (Fig 1). A gastrointestinal series exhibited some nodularity in the third and fourth portions of the duodenum with the small intestine displaced to the left. Barium enema showed no intrinsic disease of the colon but again revealed the right lower quadrant mass pressing the ascending colon anteriorly and to the left (Fig 2A, B).

OPERATIVE FINDINGS. The patient was placed on antibiotics and there was a gradual decline in his fever. With a preoperative diagnosis of a retroperitoneal tumor of unknown

variety, the patient was explored and a huge benign lymphangioma was found and resected (Fig. 3). The tumor was multiloculated and contained areas of hemorrhage and degeneration and extended throughout most of the retroperitoneal space on the right side from the pelvis up to and around the fourth portion of the duodenum and into the small intestine mesentery. The mass was excised as completely as possible, but a small amount of tissue was left in and around the sweep of the duodenum and around the superior mesenteric vessels. The patient withstood the procedure well and received four units of blood in the operating room. His postoperative course was uneventful and he was discharged on the 12th postoperative day with a well healed wound.

Pathological examination was reported as showing dilated lymphatic channels, fat laden histiocytes and focal chronic inflammation.

DISCUSSION. There are several theories as to origin of retroperitoneal lymphangiomas. They generally arise from embryonal segregation of lymphatic vessels with subsequent proliferation before birth or after. Another possibility is that they are acquired following the obstruction of existing lymphatic channels by inflammatory disease or fibrotic processes (3). These tumors are occasionally seen following radical retroperitoneal or pelvic surgery (7).

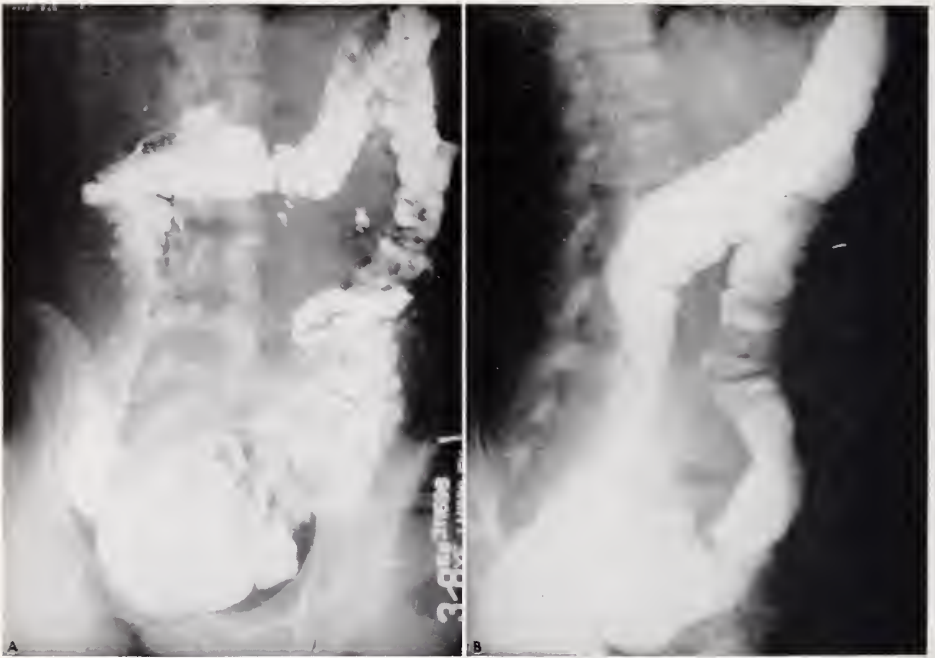
Lymphangiomas that arise in the retroperitoneal space may separate the leaves of the mesentery as they grow anteriorly and take a mesenteric position, or they may push posteriorly in their development to be recognized only as retroperitoneal growths. They may encroach on surrounding structures including gastrointestinal organs and retroperitoneal organs and lead to a mechanical obstruction (8). In this case, the right ureter was partially obstructed by the tumor which had sur-



Case No. 4, Fig. 1. Intravenous pyelogram showing a dilated right pelvis and ureter with displacement of right ureter to midline.

rounded it and there was also evidence of tumor compression on the third and fourth portions of the duodenum. Lymphangiomas are almost always benign (8) and may occur either as solitary cysts or as multilocular structures with capillary cavernous and cystic spaces containing lymph-like

material. The typical histologic characteristics of this tumor (1) is that of large cystic spaces lined by epithelium, often with thick walls containing collagen and smooth muscle in varying proportions. They occur in any age group with an even distribution and with no evident sex predilection. Most



Case No. 4, Fig. 2 A, B. Barium enema showing a retroperitoneal mass displacing the ascending colon anteriorly and to midline.



Case No. 4, Fig. 3. Cut section of tumor showing multiloculated nature of cystic mass.

patients present with an abdominal mass which causes dull pain symptoms. Mesenteric tumors often present with more acute pain symptoms and may simulate an acute abdomen. Secondary infection and hemorrhage in the cysts has been described as in the case presented.

Treatment consists of as complete excision of the tumor as possible. With extension into the leaves of the mesentery, a bowel resection may be necessary and therefore preoperative bowel preparation should be included. It is not always feasible to excise the complete tumor because of its relationship to vital structures. With incomplete removal, there is a possibility of recurrence at a later date; however even with recurrence, secondary procedures have been advocated. The slow growth of this tumor makes subsequent symptomatic recurrence unlikely for many years.

Good results have been reported with marsupialization. Simple drainage or marsupialization of a cystic lesion may be employed as the first step to total excision when it is not possible to do the excision during the first operation, but primary complete surgical

removal represents the ideal form of treatment.

SUMMARY. A case of a retroperitoneal and mesenteric lymphangioma is presented. The uncommon nature of this form of retroperitoneal tumor is emphasized and various aspects of its pathology are discussed.

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CLINICO-PATHOLOGICAL CONFERENCE

Hypercalcemia and Azotemia with Terminal Hypotension

Edited by

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A 70 year old white male was admitted to The Mount Sinai Hospital because of azotemia. Seven months prior to admission, he noted loss of appetite and constipation unresponsive to increasing doses of laxatives which he had been taking for many years. He lost approximately 20 pounds in weight over a three month period. A barium enema and upper gastrointestinal series performed by his physician were reported to be normal. He was treated with vitamin B₁₂ injections. Because of persistence of symptoms, he was referred to the Diagnostic Clinic three months prior to entry.

There were no significant physical abnormalities. The hemoglobin level was 12.1 gm/100 cc, the white blood count was 7,200/cu mm with a normal differential and the erythrocyte sedimentation rate (ESR) was 25 mm/hour. Two urine specimens had specific gravities of 1.012 and 1.006 with traces of protein and no sugar. The urinary sediment contained 10 to 12 white blood cells per high power field. The fasting blood sugar was 126 mg/100 cc and blood urea nitrogen (BUN) was 39 mg/100 cc. Serum alkaline phosphatase activity was 15.3 King-Armstrong units. An upper gastrointestinal series and barium enema were again normal. Following the cathartics he had received for the barium enema examination, he did not require further laxatives; his appetite improved and he gained 20 pounds. The BUN one month later was 24 mg/100 cc. An intravenous pyelogram showed some dilatation of the inferior calyces of the left kidney and faint excretion. The right renal shadow was not defined and no excretion was demonstrable. No calculi were seen.

Ten days prior to admittance he again noted anorexia, constipation accompanied by increasing thirst and nocturia which had not previously been present. For two days he had intermittent periumbilical crampy pain which radiated to the substernal region, unassociated with vomiting. During a previous admission to The Mount Sinai Hospital three years earlier, the patient underwent a suprapubic prostatectomy for benign prostatic hypertrophy. At that time, stones were removed from his bladder. He was told of an elevated blood pressure 15 years prior to admission, but had not received any medications. There was no history of congestive heart failure, although he had noted angina on exertion. The patient also had pulmonary tuberculosis as a child and gonococcal urethritis at 20 years of age. Cystoscopy was performed at age 45 for a urethral stricture.

The patient was oriented but drowsy and appeared chronically ill. His

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temperature was 101.6 F.; the blood pressure 160/90; the pulse rate 90/min and regular; and the respiration 16/min. Funduscopic examination revealed Grade II hypertensive changes and a few microaneurysms. The mucous membranes were dry. No masses were felt in the neck or supraclavicular areas. The thoracic spine was kyphoscoliotic and there was hyperresonance on percussion of the heart. Auscultation of the lungs was normal. The Point of maximal impulse was diffuse and a Grade II short apical systolic murmur was heard. No abdominal organs or masses were palpable and rectal examination was normal. All reflexes were active and equal. The hemoglobin level was 11.9 gm/100 cc, the white blood count 21,800 with a shift to the left. The erythrocyte sedimentation rate was 31 mm/hr; the blood urea nitrogen 87 mg/100 cc; serum creatinine 5.0 mg/100 cc; and uric acid 9.5 mg/100 cc. The serum sodium was 135 mEq/Liter; the potassium 2.7 mEq/Liter; chlorides 84 mEq/Liter; and the CO₂ 31 mEq/Liter. The urine had a specific gravity of 1.016 with a trace of protein but no sugar. Greater than 200,000 colonies/cc *Enterococcus*, sensitive to chloramphenicol, erythromycin and penicillin were cultured from the urine. An ECG revealed nonspecific ST and T wave changes. Catheterization of the bladder yielded 75 ml of urine. An intravenous pyelogram did not visualize the kidneys and no stones or contrast material were noted in the bladder. A total of 2,900 cc of one-quarter strength saline containing 120 mEq/Liter of potassium and 2 gm chloramphenicol were given intravenously over the first 24 hours. By the following morning, the patient was afebrile. On the second day he became obtunded. The BUN was 106 mg/100 cc; the serum sodium was 140 mEq/Liter; potassium 3.2 mEq/Liter; chlorides 99 mEq/Liter; and CO₂ 26 mEq/Liter. The arterial pH was 7.48; the serum calcium 15 mg/100 cc; and the serum phosphorous 4.6 mg/100 cc. Intravenous Solumedrol was instituted. Bone marrow aspiration showed no tumor cells or increase in plasma cells. The urinary output on the second day was 1,600 cc and hydration was continued. The following morning, the patient became disoriented, the blood pressure fell to 98/60 and bilateral rales were heard in the chest. The venous pressure was 70 mm of saline. A repeat serum calcium and phosphorous were 14.9 mg/100 cc and 3.8 mg/100 cc respectively. X-ray of both hands failed to show subperiosteal bone reabsorption or demineralization. Aramine was required to maintain the blood pressure; however, hypotension persisted with increasing dyspnea and cyanosis, and the patient died on the fourth hospital day in pulmonary edema.

*Dr. Gabrilove:** This 70 year old gentleman presented with azotemia, anorexia, constipation and weight loss and I presume he was thought to have a malignancy. However, a barium enema and a gastrointestinal series were normal, and he was given vitamin B₁₂, and referred to the Diagnostic Clinic. The gastrointestinal series was again normal. He was not anemic, but the erythrocyte sedimentation rate was slightly elevated. The blood urea nitrogen and the fasting blood sugar were elevated, the latter suggesting that he might be a mild diabetic. No calculi were seen on intravenous pyelography but there was slight

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dilatation on the left side and no excretion at all on the right side. Following these studies, he regained the weight he had lost, his appetite improved and he felt well. He was subsequently lost from observation.

He came to The Mount Sinai Hospital again because of anorexia and constipation, accompanied by increasing thirst, nocturia, and intermittent periumbilical cramps. The nocturia and thirst suggested that he might be becoming progressively azotemic or excreting substances that increase the osmolality of the urine, such as glucose, since we know he was a mild diabetic, or having some tubular nephropathy. In regard to the azotemia, he had several good reasons to develop renal insufficiency on the basis of pyelonephritis. He had had gonorrhea, followed by a urethral stricture. He had a suprapubic prostatectomy and, during the procedure, stones were found in the bladder. Although bladder stones are not uncommon with prostatic obstruction, the possibility of another course for the lithiasis must be borne in mind. When he was admitted he was quite drowsy, but oriented. His temperature was slightly elevated, and blood pressure was 160/90. The remainder of the examination was essentially negative, apart from mild hypertensive fundal retinopathy and a few microaneurysms. The hemoglobin was normal. The white count was elevated. This latter resulted, I think, from a urinary tract infection since he had a positive colony count, and his past history was compatible with pyelonephritis. The BUN was 87 mg/100 cc, the creatinine 5.0 mg/100 cc and the uric acid 9.5 mg/100 cc, all elevated values. The serum sodium was normal, but there was a hypochloremic hypokalemic alkalosis. This latter finding is rather unusual as an accompaniment of renal insufficiency. The specific gravity was 1.016 rather than 1.010 with only a trace of protein. Catheterization revealed a moderate amount of urinary retention and an intravenous pyelogram did not visualize the kidneys. No stones were seen.

He thus had hypertension and hypochloremic alkalosis. With these conditions one must always think of the possibility of primary aldosteronism. However the clinical picture was not that of primary aldosteronism. The patient was treated carefully with antibiotics, intravenous fluids, and was given a small amount of potassium to correct the alkalosis while further studies were carried out. In spite of a normal temperature, presumably indicating the infection was under control, he became progressively obtunded. The urea nitrogen rose, but the arterial pH was alkaline. The serum calcium was then found to be 15 mg/100 cc. The serum phosphorus was 4.6 mg/100 cc, which was not very high considering a BUN over 100 mg/100 cc. The electrolytes were now essentially normal. Certainly hypercalcemia is not a feature of primary aldosteronism. It appeared likely that the abnormality in renal function and the obtundation might be secondary to the hypercalcemia. His urinary output remained adequate, but he became disoriented, his blood pressure fell, and rales were heard in the lungs. The venous pressure was normal. He developed dyspnea and cyanosis, and on the fourth hospital day he died in pulmonary edema.

Prior to his demise, further studies to determine the cause of the hyper-

calcemia were performed. Adrenal glucosteroids did not reduce the serum level. Although x-rays of the bones were not diagnostic of hyperparathyroidism, a diagnosis of primary hyperparathyroidism must always be considered in a patient with renal insufficiency and hypercalcemia, particularly if the serum calcium level is not lowered by adrenal glucosteroids. True, secondary hyperparathyroidism may be found in patients with long standing renal insufficiency. However, this man had a short history of renal insufficiency. Further in hyperparathyroidism of a secondary nature, the serum calcium is usually low or normal, although in Pollak's series there were a number of cases that had high titers of serum calcium. However, I am not sure that all Pollak's patients had secondary hyperparathyroidism. It is quite possible some may have been instances of the primary variety, since even pathologists have difficulty in differentiating secondary from primary hyperparathyroidism. If one considers other causes for hypercalcemia, it was obvious that he did not have a milk-alkali syndrome, vitamin D intoxication, hyperthyroidism, Paget's disease, or sarcoidosis as a cause of hypercalcemia. Multiple myeloma must be considered but was excluded by the negative marrow. There was no evidence of metastatic carcinoma, but one must consider the primary carcinomas associated with hypercalcemia. Of the primary carcinomas associated with the parathyromimetic syndrome, about three-fourths of them are discovered before the serum calcium becomes elevated. Of the quarter presenting with hypercalcemia, the majority originate from the lung or the kidney. It seems unlikely on the basis of the data available that he had either of these. We can exclude the carcinomas of ovary, uterus and the vagina in the discussion of the present case, although it is possible that he might have had a tumor of the prostate, urinary bladder or pancreas. Thus, hypercalcemia and a parathyromimetic syndrome may result from both non-parathyroid and parathyroid tumors. Indeed, it has been claimed that the severest symptoms due to hypercalcemia are seen with non-parathyroid tumors. However, I do not think one can use this as a differential point. This man had many of the symptoms indicative of hypercalcemia and parathyroid intoxication and these are all rather nonspecific. Weakness, anorexia, nausea, vomiting, weight loss, fatigue, lethargy, drowsiness, confusion and bone pain are common. Abdominal pain may be due to gastrointestinal ulcerations or pancreatitis. Parathyroid adenomas have a high incidence of associated ulcer. Constipation, polyuria and polydipsia may also be present. Patients with parathyroid intoxication have a surprisingly high incidence of hypokalemia. Presumably hypercalcemia alters renal tubular function and alters the ability to conserve potassium. In addition, potassium wastage is aggravated by vomiting. Considering all the findings, the likelihood is that he had hyperparathyroidism and parathyroid intoxication. The terminal episode of untreated hypercalcemia is often shock and coma. The cause of death is not clear but I assume it must be related to the effect of the calcium on the heart.

If he had primary hyperparathyroidism of parathyroid origin, what was the underlying disorder? Statistically, a single adenoma would be most likely and

more frequently the tumor is in the lower pole. The other possibilities are multiple adenomas, hyperplasia and carcinoma. We have no evidence that this man had multiple endocrine adenomas which are associated with multiple parathyroid tumors or hyperplasia. In general hyperplasia of the chief cell variety and carcinoma are uncommon. In summary, I would like to say that the nonspecific symptoms at first suggested a carcinoma, but a malignant disease was not found. He developed a peculiar type of renal insufficiency with a hypochloremic hypokalemic alkalosis, associated with only slight elevation of the serum phosphate and a very high serum calcium. Secondary hyperparathyroidism seemed to be readily excluded, and I discard an extra-parathyroid tumor and some of the previously mentioned causes of hypercalcemia. I concluded that he had hyperparathyroidism and deposition of calcium in the kidney and resultant fibrosis and inability to concentrate the urine because of the hypercalcemia. Superimposed on this he may have had pyelonephritis from previous urinary tract disease. I believe the parathyroid disorder was a parathyroid tumor, and he died of parathyroid intoxication.

In view of this, the question arises as to the need for prompt surgical intervention. The mortality rate for untreated acute hyperparathyroidism approaches 100% whereas with surgery it has been approximately 20%. Medical therapy to reduce the serum calcium is of little value. Among the procedures suggested have been measures to increase the renal excretion of calcium (rehydration with saline, infusion of sodium sulfate, hemo- and peritoneal dialysis), measures to reduce the serum ionized calcium level (endathamil disodium, citrate, high phosphate diet) and corticosteroids. Of these rehydration with saline and perhaps large oral doses of phosphate are the most useful and practical, but only as temporizing measures. The important point is to recognize the disorder and then promptly to intervene surgically.

*Dr. Sheldon Freedman:** The kidneys weighed 150 grams each. They were not shrunken as might be expected in chronic pyelonephritis; nor were pyelonephritic scars present. On the cut surface there were small white flecks scattered throughout the renal cortex and medulla which, on microscopic section were areas of calcification. Throughout the cortex were areas of chronic inflammation, congestion, and parenchymal atrophy. Some glomeruli were hyalinized and fibrotic and many tubules were atrophic. These changes most likely resulted from nephrosclerosis. The tubules within the medulla had calcium deposition and destruction of the epithelium (Fig 1) in addition to areas of fibrosis and compensatory hyperplasia. Calcium casts were also present in the collecting tubules. A large number of polymorphonuclear leukocytes were present in the distal tubules and indicated an early ascending acute pyelonephritis. Helstrom reported that in more than half of cases of nephrocalcinosis there is a predisposition to infection.

The heart was enlarged. It weighed 480 grams. The left ventricle was hypertrophied and measured over 2 cm in thickness. There were no valvular

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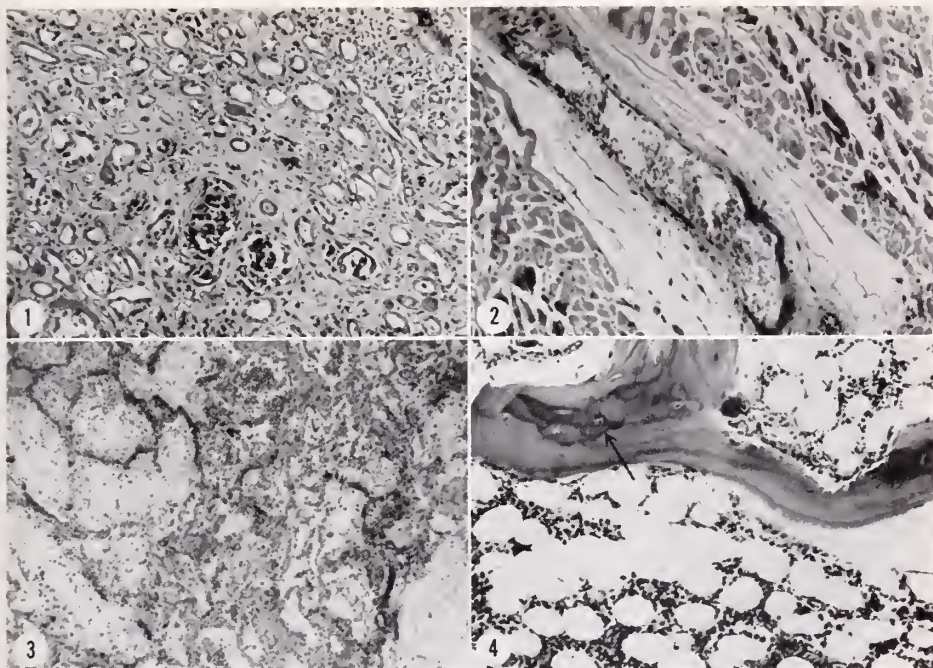


FIG. 1. Section of renal medulla showing calcification and destruction of the tubular epithelium (H & E $\times 100$).

FIG. 2. Myocardium with focal areas of calcification and calcification in the wall of a coronary vessel (H & E $\times 400$).

FIG. 3. Lung showing interstitial edema and bronchopneumonia (H & E $\times 100$).

FIG. 4. Bony trabeculae showing osteoclastic activity (arrow) (H & E $\times 400$).

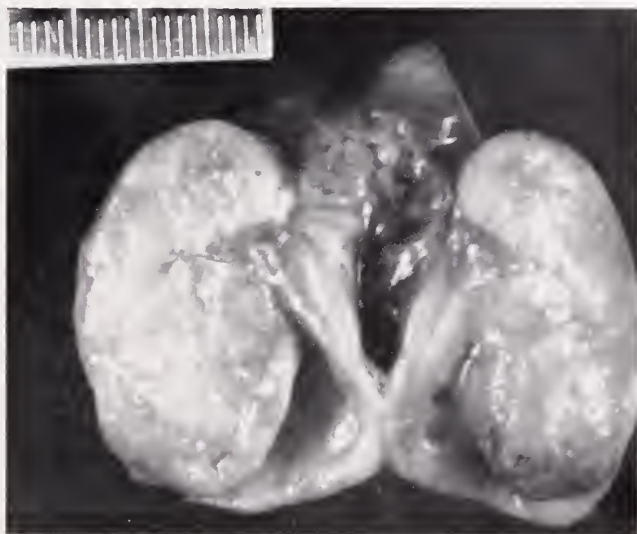


FIG. 5. Large well-encapsulated parathyroid adenoma.

lesions, but on cutting the myocardium, it appeared to be gritty and the muscle had a speckled appearance due to calcium similar to the appearance of the kidneys. Calcium was also deposited in the walls of the blood vessels of the heart as well as in all the blood vessels of the body (Fig 2). In areas within the myocardium, there was necrosis, but little inflammation and I would interpret this as representing a stage prior to calcification. The lungs were enlarged and congested and showed metastatic calcifications. The pulmonary vessels were uninvolved and no thrombi were found. Microscopically, the lungs showed extensive edema, fibrin deposition and a bronchopneumonia (Fig 3). Calcium was deposited in the walls of the pulmonary arteries and extensive

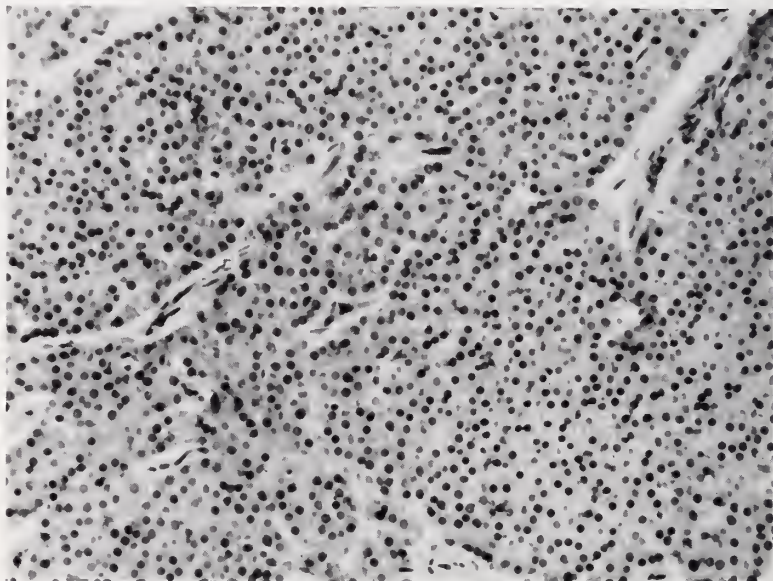


FIG. 6. Microscopic section of parathyroid adenoma showing a uniform pattern of chief cells (H & E $\times 400$).

calcification was found in the alveolar septa. The bones were soft and showed early osteoporosis as evidenced by increased osteoclastic erosion of the bony trabeculae. The cellular elements of the bone marrow were normal (Fig 4). Within the right lobe of the thyroid was a well encapsulated parathyroid adenoma about the size of a walnut (Fig 5). The tumor appeared pale and had a homogeneous reddish-brown appearance (Fig 6). The remaining parathyroid glands were small and showed no evidence of hyperplasia. As Dr. Gabrilove pointed out, secondary hyperparathyroidism can imitate many diseases. Even the bone lesions that were present can be imitated by secondary hyperparathyroidism. However, in most cases, the presence of three normal parathyroid glands negates the possibility of secondary hyperparathyroidism. Microscopically, this tumor was predominantly composed of chief cells. There were almost no oxyphilic cells and the fat cells normally found in the parathyroid glands were absent.

Are there any questions?

Question: To what extent did the calcium deposition in the myocardium contribute to the heart failure?

Dr. Freedman: In the reported cases where necrosis was found, arteriosclerosis was also present. So I would hesitate to say that calcium by itself produced the necrosis or heart failure.

Dr. Gabrilove: It is difficult for me to accept that the patient's heart failure was due to arteriosclerosis. I don't know the mechanism of heart failure associated with hypercalcemia, but apparently it is so common in hyperparathyroidism that it must have something to do with the hypercalcemia. Hypercalcemia may exert a direct effect on the cardiac muscle.

Question: Dr. Gabrilove, could you comment on the status of the calcitonin?

Dr. Gabrilove: Calcitonin apparently is a true hormone derived from parathyroid or the thyroid (thyrocalcitonin) or both, which reacts to reduce the serum calcium.

Final diagnosis:

1. Parathyroid adenoma
Metastatic calcification of the heart, kidney, and lungs
Nephrocalcinosis
Osteoporosis, mild
2. Hypertensive cardiovascular heart disease
3. Acute bronchopneumonia

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RADIOLOGICAL NOTES

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CASE NO. 272

A 70 year old man was admitted to the hospital complaining of anorexia, weight loss and weakness of two months' duration. Occupational history revealed intermittent contact with asbestos over a period of many years while engaged in roofing activities. Pertinent physical findings on admission included a moderately enlarged, firm liver and some moist râles at the lung bases.

Chest x-ray revealed bibasilar interstitial and nodular shadows of moderate degree compatible with long standing fibrosis, but some acute pneumonic infiltration could not be excluded. Gastrointestinal series was performed (Fig 1, 2). Numerous round, smooth nodules were demonstrated in the gastric mucosa or submucosa, ranging in size up to 1.5 cm in diameter. Many of these lesions showed a central collection of barium which gave the appearance of a target or "bull's eye." The radiographic features were those of rapidly proliferating sarcomatous nodules with central ulcerations. Innumerable smaller nodular shadows were seen throughout the jejunum and to a lesser extent in the ileum. There was evidence of a retrogastric mass with forward displacement of the body of the stomach and straightening of the lesser curvature. Melanosarcoma and lymphosarcoma were considered in the differential diagnosis.

Four weeks after admission, the patient suddenly developed diffuse abdominal pain with advancing signs of peritoneal irritation. Free air was seen beneath the leaves of the diaphragm on an erect abdominal radiograph and a perforated viscus was diagnosed. Exploratory laparotomy was performed. A small perforation of the ileum was discovered, and a number of areas of "impending perforation" were identified in the adjacent bowel wall. There was a generalized peritonitis secondary to the bowel perforation. Peripancreatic and perigastric lymph nodes were markedly enlarged. Each lobe of the liver contained a huge tumor mass. A segmental small bowel resection was performed with end to end anastomosis and the enlarged lymph nodes were biopsied. The abdomen was drained and closed.

The pathologist described a 6 cm segment of ileum which had an 0.5 cm perforation in the center of a much larger zone of ulceration; four additional smaller zones of ulceration were present in the same specimen. Microscopic examination of the ulcerated bowel wall and the lymph nodes revealed reticulum cell sarcoma.

The patient had a stormy postoperative course. He developed profound unresponsive hyponatremia, massive gastrointestinal bleeding, gram negative sepsis and pulmonary complications. He died on the fifteenth postoperative day. Post mortem examination was not performed.

DISCUSSION

See discussion following Case No. 274.

Case Report: RETICULUM CELL SARCOMA INVOLVING STOMACH AND SMALL BOWEL.



Case 272, Fig. 1. Gastrointestinal series reveals numerous nodular filling defects in the barium filled stomach (arrows). They appear to be submucosal or possibly mucosal in location and range in size up to 1.5 cm in diameter. An exquisite central collection of barium, seen in many of the nodules, creates the appearance of a target or a "bulls-eye." This represents an ulceration in the necrotic center of a rapidly proliferating sarcomatous lesion.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Mansho T. Khilmani, The Mount Sinai Hospital, New York, N.Y.

CASE NO. 273

A 63 year old woman was admitted to the hospital complaining of vomiting, girdle-like abdominal pain and temperature to 103 F., of three days duration.

Three months previously, the patient presented with a history of marked weight loss, nausea and epigastric pressure. A complete gastrointestinal evaluation at another institution revealed radiographic abnormalities in the upper gastrointestinal tract. Symptomatic therapy produced no relief; weight loss



Case 272, Fig. 2. Radiograph from same gastrointestinal series again demonstrates the gastric lesions (arrows). In addition, one can identify numerous tiny filling defects which distort the expected feathery mucosal pattern of the jejunum. These defects were present on a number of films.

continued and severe anemia developed. Current symptoms started suddenly after a meal three days prior to admission and were unremitting. Examination revealed a chronically ill, wasted female, in acute distress. There was generalized abdominal tenderness but no other pertinent positive physical findings were noted.

Hemoglobin level ranged from 7.3 to 12.4 gm, 100 cc with transfusion ther-



Case 273, Fig. 1. Postero-anterior radiograph from gastrointestinal series reveals abnormal appearance to jejunal loops. The normal feathery mucosal pattern is absent, replaced by a moulage. Where visualized, the folds are thickened and blunted. The question of some extrinsic nodular defects is raised but not confirmed on additional views.

apy. The stool contained an excessive amount of fat. Radiographic examination of the chest and colon showed no unusual feature. Gastrointestinal series revealed abnormal findings in the duodenum and jejunum (Fig 1-4). The fold pattern was gross and thickened in the duodenum and proximal jejunum, with the normal feathery pattern first appearing in the distal jejunum. The question of nodular impressions of the bowel was raised but could not be confirmed; there was some extrinsic pressure on the postbulbar duodenum, however. The barium presented an amorphous moulage appearance and there was

mild delayed segmentation. There was no dilatation. A definite mucosal lesion was not identified. The spleen appeared slightly enlarged. The appearance was similar to that seen on the study made three months previously and exhibited many features of a malabsorption pattern.



Case 273, Fig. 2. Lateral view shows a distensible duodenal bulb. A few thickened folds are noted and a fine feathery mucosal pattern is not seen.

Exploratory laparotomy was performed. Enlarged lymph nodes were seen in the mesentery of the proximal small bowel and biopsy was performed. The mesentery of the more distal small bowel was normal. The bowel wall was normal to palpation throughout. The liver and spleen were not enlarged. Histologic examination of the lymph nodes revealed reticulum cell sarcoma. The patient was referred to another institution for definitive therapy.



Case 273, Fig. 3. Mid-way in examination, normal feathery mucosal pattern first appears in the distal jejunal loops occupying the mid- and lower abdomen. Again, upper jejunal loops have a bizarre appearance. Only a few thickened folds are seen in descending duodenum.

DISCUSSION

See discussion after Case No. 274.

Case Report: RETICULUM CELL SARCOMA INVOLVING LYMPH NODES OF SMALL BOWEL MESENTERY.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Thomas Cassara, Good Samaritan Hospital, Suffern, New York.



Case 273, Fig. 4. Late in examination, some normal-appearing ileal loops are filled. There is no dilatation.

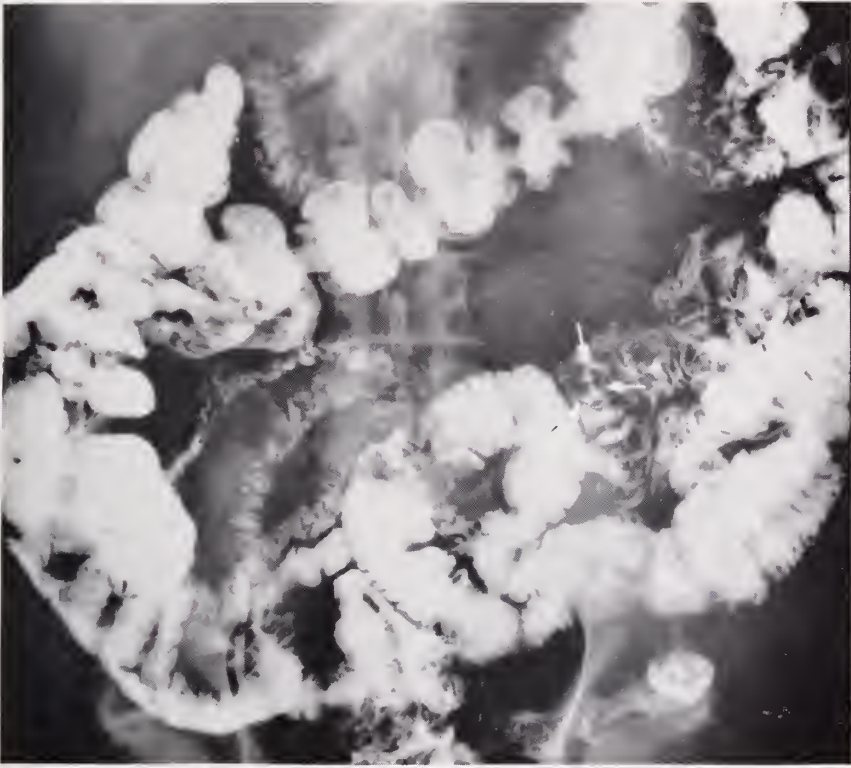
CASE NO. 274

No clinical history is available.

DISCUSSION

Cases 272, 273 and 274 demonstrate some less common gastrointestinal manifestations of sarcomata. Melanosarcoma (Case 274) has a propensity for metastasizing to the gastrointestinal tract and may produce the picture of multiple submucosal nodules. The tumors are very cellular, grow rapidly in size and encourage no desmoplastic reaction: There is a tendency toward central necrosis and ulceration. The target, "bull's-eye," or doughnut appear-

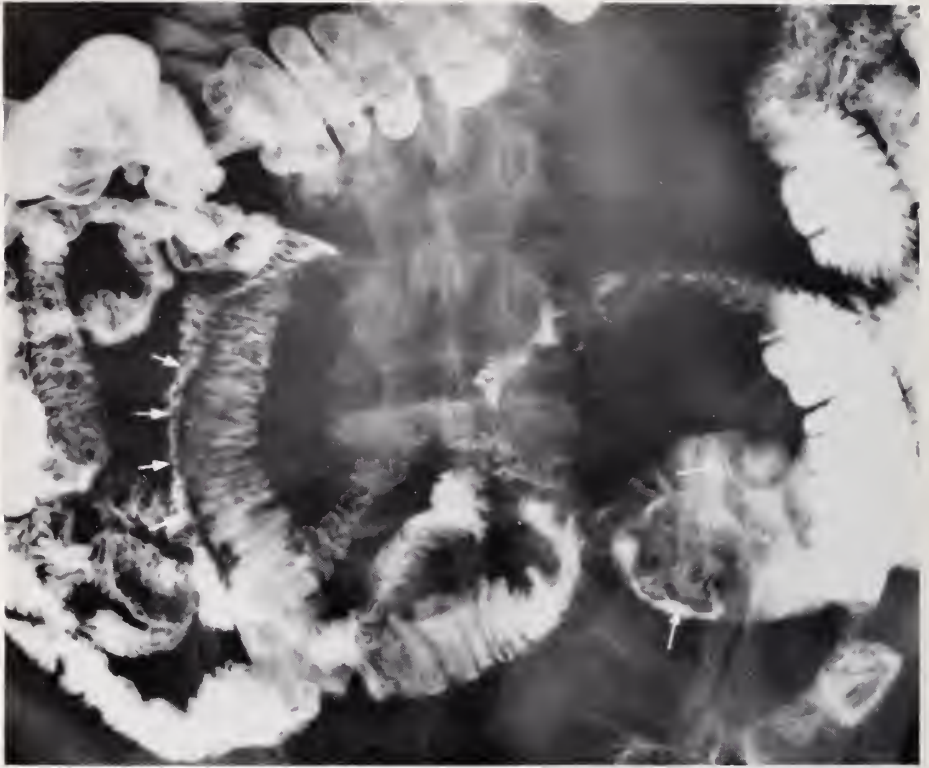
ance is produced when barium fills the depressed central ulceration and surrounds the smooth periphery leaving a circular lucency between. Although most often seen with melanosarcoma, this appearance is not pathognomonic but also occurs in other rapidly growing cellular neoplasms such as reticulum cell sarcoma (Case 272) and anaplastic carcinoma.



Case 274, Fig. 1. Small bowel examination reveals numerous discrete nodular lesions within jejunum. Their contours are sharp and slightly lobulated and some, when seen "en face," contain central ulcerations (between arrows). Similar polypoid masses with ulcerations are seen in ileum (lower arrow).

In Case 273, reticulum cell sarcoma involved the lymph nodes in the small bowel mesentery and resulted in clinical steatorrhea and radiographic features of a malabsorption pattern. Although the possibility of nodular indentations on the bowel was raised, this was not confirmed radiographically or at laparotomy. Further, the bowel wall was not abnormal to palpation; unfortunately, no biopsy of the bowel was performed at surgery or perorally. Nevertheless, the altered mucosal pattern, moulage, and mild delayed segmentation are reminiscent of sprue although dilatation—the hallmark of sprue—is absent.

Case Report: MELANOSARCOMA WITH GASTRIC AND SMALL BOWEL METASTASES.



Case 274, Fig. 2. The ileal lesions are again noted. Some have a shallow central ulceration (upper arrow); others assume a grape-like cluster formation of polypoid masses (lower arrow). In distal ileum a loop of bowel is indented in pleat-like manner by an adjacent mass (along arrows).

CASE NO. 275

An 80 year old man was admitted to the hospital with complaints of weakness, temperature to 102 F., and bilateral flank pain of two days duration.

Five years prior to admission the patient underwent an abdomino-perineal resection for adenocarcinoma of the rectosigmoid. Eight mesenteric lymph nodes were negative histologically for metastatic tumor. Since that time, intermittent functional colostomy problems were controlled symptomatically. Two transurethral prostatic resections were performed for obstructive urinary symptoms. A number of episodes of cystitis and pyelonephritis had been treated with appropriate antibiotic therapy. Eight months prior to admission a bout of painless obstructive jaundice occurred. Jaundice abated spontaneously and a definite etiological diagnosis was not established. Oral cholecystogram was performed initially and was unsuccessful. When jaundice subsided, intravenous cholangiogram was performed which revealed no definite abnormality of the common duct system or gall bladder.

The clinical impression on admission was that of a cachectic, pre-terminal old man. The liver was enlarged, hard and lumpy, felt to be characteristic of metastatic malignant disease. Signs and symptoms of severe urinary tract infection did not respond to antibiotic therapy, catheter drainage and sup-



Case 275, Fig. 1. Coned down view of right upper quadrant reveals innumerable fine punctate psammoma-like calcifications within medial aspect of hepatic outline.

portive measures. The clinical picture was one of septicemia. The patient died; post-mortem examination was not obtained.

Radiographic studies of the urinary tract performed during the final admission had revealed a number of areas of finely speckled calcification in the right upper quadrant, apparently in the liver (Fig 1). These were felt to represent calcifying foci of metastatic malignant disease. Previous radiographs were reviewed. Calcifications were not present eight months previously when studies of the biliary tract were performed. Those studies included coned spot films as well as laminograms and were of good technical quality.

DISCUSSION

Until 1961, only four cases of calcified liver metastases were described in the literature. Khilnani published two additional cases and reviewed the literature (1). Since then, additional cases of colonic carcinomas with calcified hepatic metastases have been reported. The characteristic findings are stippled fine punctate calcific densities deposited within the liver in clumped fashion. Other similar intrahepatic calcifications exist in primary hepatomas in children. These differ, however, from the coarser calcifications of disseminated tuberculosis and the ring-like calcifications of cysts and abscesses.

Case Report: CALCIFYING HEPATIC METASTASES FROM COLONIC ADENOCARCINOMA.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. A. Z. Freudenheim, Good Samaritan Hospital, Suffern, New York.

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Computer Analysis of the Electrocardiogram: A Joint Project

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AND DAVID ALEXANDER,** B.S.E.E.

INTRODUCTION

During recent years, advances in computer technology in medicine (1-4) have stimulated intensive research in the analysis of the electrocardiogram (ECG) by digital computer. Cardiologists have teamed with systems analysts, programmers and electrical engineers for the purpose of achieving the goal of successful application.

For complete clinical acceptance, it is required that the computer electrocardiographic analysis perform all the functions of the electrocardiographer accurately, automatically and with dispatch; including interpretation of cardiac rhythm, rate, and diagnosis of the other abnormalities of the electrocardiographic signal. Furthermore, the tracings should be stored for later retrieval for comparison of serial records, and should also be readily obtainable on demand.

At present, there is no generally available program for computer analysis of the electrocardiogram for routine application which performs all of the aforementioned functions. The degree of sophistication of available programs is extremely variable and spans the extremes, from technician hand measured tracings for data input (5) to the automatic system of Caceres et al (6) with direct telephone data transmission. Utilizing the method of Fourier analysis for the study of electrocardiographic patterns, Cady et al (7) have reported a digital computer program for left ventricular hypertrophy. This work was presented as an example of the application of computer techniques for the mass screening of electrocardiograms with a possible processing of one thousand records per hour.

For the past year, a joint feasibility study project for digital computer analysis of the electrocardiogram has been undertaken at The Mount Sinai Hospital in association with the Advanced Systems Development Division of the International Business Machine Corporation. A prototype system had been under development for three years and was presented by Wortzman et al (8) in 1965. At first this system was utilized, but the results of feasibility testing against

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the cardiologists' independent analysis was considered not to be entirely satisfactory. Therefore, the entire arrhythmia and measurement program was rewritten completely and a report will be made of the initial results.

METHODS OF PROCEDURE

The present experimental system operating now at The Mount Sinai Hospital is oriented about an IBM 1401 computer. The actual data flow is illustrated in Figure 1. After the request has been forwarded to the technician, the system commences with the patient being prepared in the identical way in which trac-

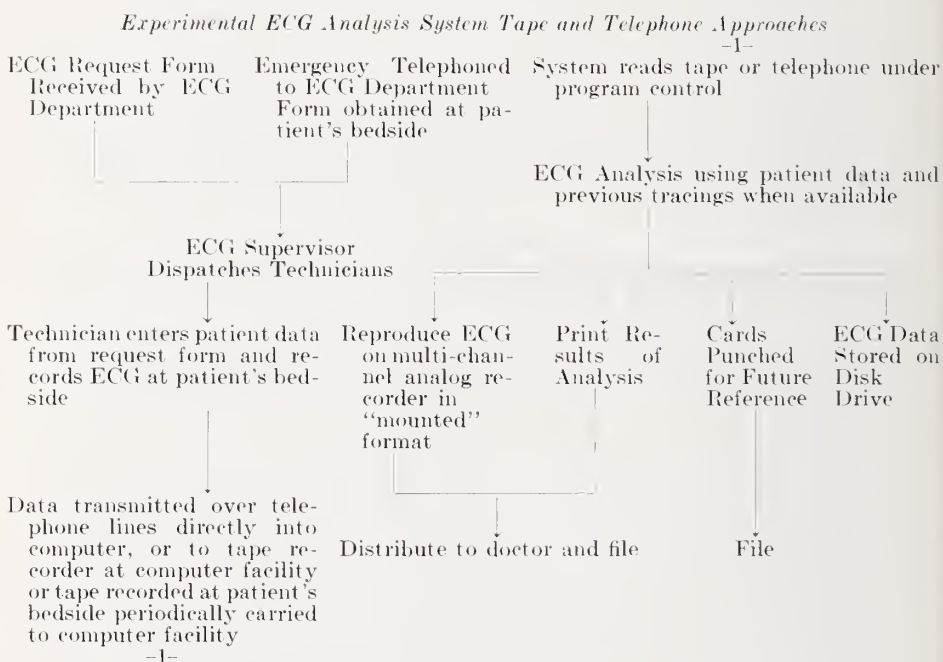


FIG. 1. Data flow.

ings are taken customarily, utilizing the routine five-lead ECG cable. However, the leads are recorded on a specially designed data gathering cart.

EXPERIMENTAL ECG DATA GATHERING CONSOLE

A portable console* (of which two are in present use here) contains a strip-chart recorder, an ECG preamplifier, ECG lead-selector switches, acoustical coupling, timing circuits, and a frequency modulator (Figure 2). The acoustical coupling allows for telephone transmission from the bedside over telephone lines through the standard telephone handset. The purpose of the frequency modulator is to shift the bandwidth of the ECG from the low end of the spectrum to a portion more suitable for magnetic tape recording and telephone transmission. The carts carry a tape recorder for use in areas of the hospital

* IBM "9x31" Experimental ECG Data Gathering Console

which do not have a bedside telephone. The inclusion of flutter compensation permits the use of an ordinary audio tape recorder. In addition, the carts contain special thumb wheels for numeric input of the patient's hospital number and location, age, sex, date, clinical diagnosis and drugs which he may be taking. This information is also recorded on a special form (Figure 3) for the independent interpretation of the electrocardiogram by the cardiologists during our present study.

DATA COLLECTION

At the bedside, the technician enters the hospital number and other pertinent information by using the thumb wheels and then records two rhythm strips (each for 20 seconds) and the routine 12 lead electrocardiogram (each lead for 6 seconds) after suitable monitoring of the leads to determine technical acceptability. Pressing of the automatic sequence start key turns on the tape recorder and strip chart and records the ECG lead identification, a standardization pulse for each lead, followed by the ECG lead data, and then turns off the strip chart and tape recorder.

COMPUTER FACILITY

In addition to the 1401 IBM Data Processing System (Figure 4), the computer facility at present includes an additional tape recorder to record incoming data via telephone and to read data from tape for processing under program control. There is also an AT&T automatic phone answering device which answers the phone and routes the signal to the tape recorder or directly to the computer. There is an experimental analogue preprocessor which flags selected points of interest in the tracing, such as peaks and onset of waves (P, QRS, T, etc.). The preprocessor unit also contains controls for starting and stopping the tape recorder for each lead when transmitted via telephone. The analogue-to-digital (and digital-to-analogue) converter is attached to this unit.

The technician prepares the facility for processing by insertion of a seven punch card deck (Figure 4, J) with appropriate starting instructions. With the computer now in ready position, there is no need for a console operator since the entire procedure is completely automatic. The ECG signal as received in analogue form is digitized and then reconverted to analogue form and recorded by the multichannel strip chart apparatus for "mounted" ECG records (Figures 5B, 6B, 7B, 8B and 9). On the basis of significant slope changes of the ECG curves, the pertinent peak points are selected and the entire data in digital form are then analyzed according to the computer program.

DATA ANALYSIS

The "mounted" 6-channel ECG recording is accompanied by a printout presenting the computer-derived interpretation (Figure 5A, 6A, 7A and 8A). This *computer* interpretation starts with the "mounting on chart number" (see p 77), the date of recording and pertinent patient information (identification number, age, sex, drugs, clinical diagnosis, hospital location and record-

* IBM "9x12" Experimental A/D and D/A Converter

ing technician number). The printed "rhythm analysis" is a detailed statement concerning the cardiac rate and rhythm, including any abnormalities which may be present. Since rhythm alterations may exist in any of the routine 12 leads and possibly not in the two rhythm leads, the final rhythm statement is based on analysis of *all* of the 14 leads.

The rhythm analysis statements are the result of a formidable program and represent a distinct advance over the simple types of computer electrocardio-

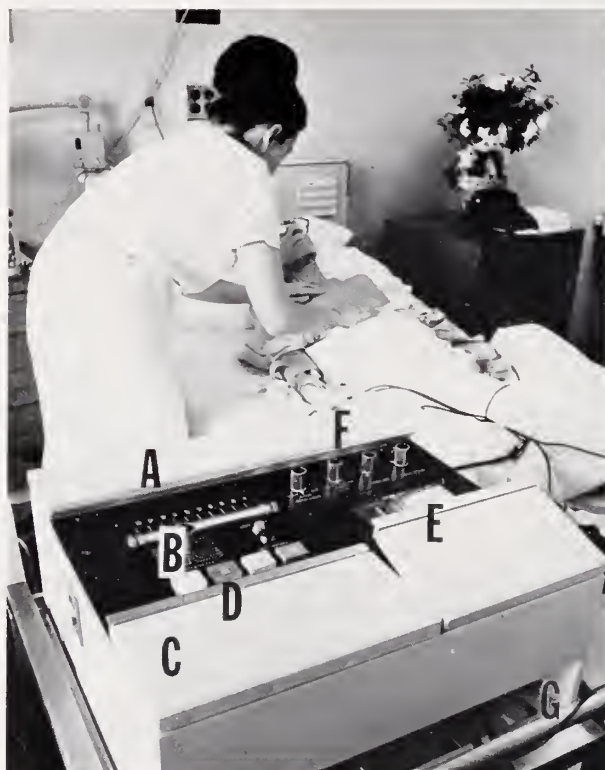


FIG. 2. IBM Experimental ECG Data Gathering Cart. Technician is recording tracing at patient's bedside in the routine manner. A—Thumb wheels; B—ECG lead selector switch; C—Receptacle for telephone handset; D—Automatic sequence start key; E—Strip chart recorder; F—Strip chart controls; G—Analogue recording tape unit.

gram "rhythm" printouts available currently. After completion of the rhythm analysis for each of the leads, a weighted point system has been employed to select and print the correct diagnosis from the many possible rhythm statements available. Furthermore, after a dominant rhythm is decided upon and other arrhythmias are also detected, then *multiple* rhythm statements will be printed (Figure 6A). On the other hand, if the diagnosis of a lead were to be "atrial fibrillation" because of absent P waves (P vector perpendicular to a lead as in lead AVL in Figure 5B) and if all other leads disclosed "normal sinus rhythm," the former diagnosis would be disregarded as incorrect by the

point system; the final rhythm statement would read "normal sinus rhythm." Conceivably a brief stretch of atrial fibrillation might thus be omitted in the final rhythm statement but other transient arrhythmias such as runs of premature beats, ventricular tachycardia, etc. would be mentioned. In the event that an arrhythmia cannot be diagnosed with certainty, as is occasionally encountered clinically, a "special message" will be printed. For example, if

COMPUTER ANALYSIS OF THE ELECTROCARDIOGRAM

The Cardiographic Laboratory, The Mount Sinai Hospital, New York 29, N. Y.

Patient _____	Date _____	Technician _____	Computer _____
Hospital # _____	Location _____	Number _____	EKG # _____
		Age _____	Sex _____

DIAGNOSIS: LEFT DIGIT

0. None _____
1. Pericardial Effusion and/or Chronic Pericarditis _____
2. Acute Myocardial Infarction _____
3. Uremia and/or Electrolyte Disturbance _____
4. Chest Pain _____
5. Coronary Insufficiency _____
6. Myocarditis _____
7. Digitalis Intoxication _____
8. ASHD _____
9. Hypertension (LVH) _____

DIAGNOSIS: RIGHT DIGIT

0. None _____
1. Pericarditis, Acute _____
2. Congenital Heart Disease _____
3. Acute RHD _____
4. Cardiac Surgery _____
5. Cor Pulmonale, acute (Pulm. Embolism) _____
6. Cor Pulmonale, Chronic (RVH) _____
7. Hypothyroid (Myxedema) _____
8. Chronic RHD _____
9. Hyperthyroid _____

DRUGS: 0. None _____

1. Digitalis _____
2. Quinidine _____
3. Hypokalemia _____

4. Digitalis and Quinidine _____

5. Fuadin _____
6. Hyperkalemia _____
7. Hypocalcemia _____

METHOD: Tape Only _____ Telephone to Tape _____ Direct and on Tape _____

INTERPRETATION:

Rhythm _____	Rate _____
Axis _____	P Waves _____ PR Interval _____
QRS Complex _____	
ST SEGMENT _____	T Waves _____
QT INTERVAL _____	U Waves _____

CONCLUSION: _____

COMPARISON WITH COMPUTER ANALYSIS: _____

INTERPRETED BY: _____

COMMENTS: _____

FIG. 3. Form for Feasibility Study.

the atrial mechanism were obscure in a tachycardia tracing, a message as to "supraventricular paroxysmal tachycardia" would appear and the various possible mechanisms would be listed.

The printed ECG measurements for the 12 leads are: the heart rate (HR) and the interval durations in seconds (P—R, Q—T, QRS; all the peak-to-peak intervals such as I—Q where I is the point of QRS onset, Q—R, R—S, S—RP where RP indicates R prime, RP—SP where SP is S prime, RJ where J is onset of ST segment; FWW which is the first wave width of QRS; and LWW

which is the last wave width of QRS). The wave *amplitudes* are printed next with JJ (J junction) which is the onset of the ST segment, QRSTA which is the QRST area and QRSA which is the QRS area. These are followed by overall ECG interval measurements and the mean frontal plane vector angles of the QRS, T, P waves, QRST (ventricular gradient) and J (onset of ST segment). The diagnostic logic utilizes this set of measurements to arrive at the final clinical statements at the bottom of the printed interpretation.



FIG. 4. IBM 1401 COMPUTER SYSTEM: A—six channel ECG recorder; B—Analogue Tape Unit; C—Experimental Analogue to Digital Converter; D—Viewing Oscilloscope; E—1406 Storage Unit; F—1402 Card Reader; G—1401 Central Processing Unit; H—1311 Magnetic Disk Storage Unit; I—1403 Printer; J—Technician initiates automatic processing with punch card deck.

There is an advantage in having available all of the parameter measurements as well as the diagnostic statements in the computer printout. In the borderline areas in clinical electrocardiography where wide disagreement exists as to the clinical significance of minor ST segment depressions and low T waves, the clinician need not accept the diagnostic conclusions stated in the computer printout. If he differs with the computer analytic statements, he may refer to the table of measurements and alter the final conclusion in accordance with his own clinical experience. Immediately preceding a diagnostic conclusion, the printout mentions only the minimal criterion or criteria

which justified that diagnosis and omits other criteria which may also have been present.

The automatically "mounted" 6-channel strip-chart recordings for each computer interpretation have been reduced photographically for publication and are of two types: one containing all ECG data on the patient (Figures 5B, 6B, 7B and 8B) and one containing the customary 12 leads in shortened form suitable for framing to fit the 8½ inch page width of the hospital charts (Figure 9). The mounted ECG records are identified at the left of each tracing by a square wave for each channel which is interpreted as a "1" if the wave is positive and a "0" if the wave is negative. A six digit binary number is obtained by reading these square waves from top to bottom and this corresponds to the "mounting on chart number" at the top of each computer printed interpretation. Thus in figure 5A the "mounting on chart number" 100110 indicates that in figure 5B the square wave is positive in the first channel, and negative in the second and third channels, and so forth.

The "mounted" strip ECG recordings are of 14 leads. From left to right and from top to bottom are longer "rhythm" recordings of leads CR₂ and II and shorter recordings of leads I, II, III, AVR, AVL, AVF and V₁ through V₆. A one centimeter (or a ½ centimeter) standardization pulse precedes the recording of each lead.

Figures 5A and 5B represent the computer interpretation and ECG tracing on a normal adult male. The term "normal measurements" will be printed only in the absence of any other diagnostic statement. In Figures 6A and 6B, the computer printout concerns a 62 year old man with chronic rheumatic heart disease and acute anteroseptal wall myocardial infarction. The rhythm analysis of "atrial fibrillation" results in omission of any P or P—R information in the ECG parameter measurement section, since such information would not be applicable. The presence of ventricular premature systoles with probable single parasystolic focus are noted. The nonspecific ST (J) depressions and T inversions are diagnosed and the possibility of concomitant lateral wall infarction is considered. Note that a definite statement of anteroseptal infarction is not made on the basis of ST segment elevation alone (4.8 mm ST elevation in lead V₃, which is one-half normal standardization). However, the diagnosis is made unequivocally when significant Q waves are detected in the same leads. The program should be modified to combine the two observations with a single diagnostic conclusion. Furthermore, although the age of any infarction is indeterminate on the basis of a single record, the diagnosis should state that the elevated ST segment suggests recent infarction, although it may also occur with ventricular aneurysm.

Figure 7A represents the computer printout for a 77 year old white woman who entered the hospital for breast surgery with digitalis intoxication. An ECG at that time disclosed 2:1 A-V heart block; right bundle branch block and abnormal left axis deviation. Despite discontinuation of digitoxin, the patient developed 3:1 A-V block, far advanced A-V block and finally com-

MOUNTING ON CHART NUMBER 100110
MOUNT SINAI HOSPITAL IBM EXPERIMENTAL AUTOMATIC ECG INTERPRETATION

MAY 18, 1966

THIS PRINTOUT IS FOR EXPERIMENTAL USE ONLY AND SHOULD NOT BE USED IN PLACE OF AN ECG INTERPRETATION BY A CARDIOLOGIST.

PATIENT NUMBER AGE SEX DRUGS CLINICAL DIAGNOSIS
000708 42 MALE NONE NORMAL

LOCATION TECHNICIAN
4000525 1

•• RHYTHM ANALYSIS ••

NORMAL SINUS RHYTHM

ECG MEASUREMENTS

LEAD NOS.	HR	INTERVALS IN SECONDS										AMPLITUDE IN TENTHS OF A MILLIVOLT										P	T		
		P-R	Q-T	QRS	I-Q	Q-R	R-S	S-RP	RP-SP	RJ	P	T	FWW	LWW	JJ	QRSTA	-Q	R	-S	RP	-SP			QRSa	
I	84	.131	.336	.069	.000	.031	.000	.000	.000	.038	.075	.176	.069	.069	00.3	04.6	00.0	06.1	00.0	00.0	00.0	00.0	04.2	00.5	01.8
II	81	.152	.327	.081	.013	.035	.020	.000	.000	.014	.119	.153	.017	.015	00.4	04.5	00.9	09.7	00.8	00.0	00.0	00.0	04.2	01.1	01.7
III	83	.152	.242	.063	.000	.035	.013	.000	.000	.016	.110	.073	.046	.007	00.7	02.4	00.0	04.9	00.5	00.0	00.0	00.0	02.2	00.8	00.8
AVR	85	.154	.331	.074	.000	.008	.034	.023	.000	.010	.099	.172	.011	.014	-00.2	-03.5	00.0	00.5	07.6	00.6	00.0	-03.5	-00.7	-01.8	-01.8
AVL	77	.334	.053	.000	.018	.000	.000	.000	.000	.035	.149	.052	.052	00.1	01.2	00.0	02.3	00.0	00.0	00.0	00.0	00.0	01.1	01.1	01.1
AVF	81	.136	.376	.076	.013	.033	.017	.000	.000	.012	.101	.159	.016	.014	00.1	02.9	00.8	06.8	00.9	00.0	00.0	00.0	02.7	01.2	01.2
V1	82	.147	.339	.093	.000	.020	.027	.000	.000	.046	.050	.156	.023	.070	-00.2	-03.9	00.0	00.9	06.0	00.0	00.0	-03.9	00.7	-01.1	-01.1
V2	82	.147	.339	.091	.000	.028	.026	.000	.000	.037	.051	.192	.033	.056	00.4	-06.1	00.0	03.4	13.3	00.0	00.0	-06.3	00.7	04.3	04.3
V3	80	.361	.086	.000	.033	.020	.000	.000	.000	.032	.072	.213	.044	.032	01.0	02.8	00.0	11.2	07.8	00.0	00.0	02.4	00.6	05.0	05.0
V4	81	.125	.343	.090	.031	.020	.000	.000	.000	.030	.072	.211	.009	.031	00.2	07.4	00.6	17.8	04.5	00.0	00.0	06.7	00.6	05.1	05.1
V5	79	.151	.355	.082	.010	.033	.029	.000	.000	.011	.106	.168	.011	.018	00.1	08.3	00.8	15.9	00.8	00.0	00.0	07.7	00.5	03.4	03.4
V6	82	.158	.358	.070	.010	.032	.000	.000	.000	.028	.119	.154	.013	.056	00.0	06.8	00.6	11.5	00.0	00.0	00.0	06.3	00.5	02.5	02.5

OVERALL INTERVALS

QRS P-R Q-T T P
.082 .145 .337 .172 .099

VECTOR ANGLE VALUES

QRS T P QRST J
045 063 070 C45

NORMAL MEASUREMENTS

FIG. 5A. Computer Printout: Normal Adult Male HR = heart rate, Intervals in seconds: I-Q = point of QRS onset to nadir of Q; Q-R = nadir of Q to summit of R; R-S = summit of R to nadir of S; RP = R prime; SP = S prime; RJ = R to J point onset; FWW = first wave width of QRS, and LWW = last wave width of QRS; JJ = onset of the ST segment; QRSTA = QRST area; QRSa = QRS area. Vector Angle Values = frontal plane vector angles of QRS, T, P waves; QRST (ventricular gradient) and J (onset of ST segment).



FIG. 5B. ECG Recording: Normal Adult Male.

THIS PRINTOUT IS FOR EXPERIMENTAL USE ONLY AND SHOULD NOT BE USED IN PLACE OF AN ECG INTERPRETATION BY A CARDIOLOGIST.

PATIENT NUMBER 269084	AGE 62	SEX MALE	DRUGS NONE	CLINICAL DIAGNOSIS CHRONIC RHEUMATIC HEART DISEASE	LOCATION 0600305	TECHNICIAN I
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•• RHYTHM ANALYSIS ••

ATRIAL FIBRILLATION WITH VENTRICULAR PREMATURE SYSTOLE

THE VENTRICULAR PREMATURE SYSTOLES HAVE VARIABLE COUPLING AND ARE PROBABLY DUE TO A SINGLE PARASYSTOLIC FOCUS.

ECG MEASUREMENTS

LEAD NDS.	••		INTERVALS IN SECONDS										••		AMPLITUDE IN TENTHS OF A MILLIVOLT										P	T
	HR	P-R	Q-T	QRS	I-Q	Q-R	R-S	S-RP	RP-SP	RJ	P	T	FWW	LWW	JJ	QRSTA	-Q	R	-S	RP	-SP	QRSA				
I	85	•	•329	•074	•028	•027	•000	•000	•000	•020	•	•117	•032	•040	•00.3	00.9	00.6	03.2	00.0	00.0	00.0	01.0	•	•00.3		
II	85	•	•318	•080	•000	•027	•000	•000	•000	•053	•	•118	•073	•073	•00.6	01.9	00.0	02.5	00.0	00.0	00.0	01.8	•	•00.6		
III	84	•	•329	•077	•000	•025	•025	•015	•000	•012	•	•146	•038	•018	•00.4	00.8	00.0	02.5	02.1	01.7	00.0	00.8	•	•00.9		
AVR	81	•	•354	•060	•032	•000	•000	•000	•000	•028	•	•155	•055	•055	00.4	•01.9	02.0	00.0	00.0	00.0	00.0	•01.1	•	•00.4		
AVL	88	•	•163	•075	•019	•026	•018	•000	•012	•	•040	•027	•012	00.3	•00.0	01.5	02.6	00.8	00.0	00.0	00.0	00.2	•	•00.3		
AVF	87	•	•331	•082	•000	•025	•024	•015	•000	•018	•	•160	•040	•016	•00.7	00.8	00.0	02.0	01.1	01.3	00.0	00.8	•	•00.9		
V1	85	•	•264	•102	•070	•000	•000	•000	•000	•031	•	•166	•099	•099	00.5	•17.7	09.2	00.0	00.0	00.0	00.0	•09.1	•	•01.2		
V2	85	•	•300	•094	•054	•000	•000	•000	•000	•039	•	•165	•088	•088	02.9	•39.5	22.1	00.0	00.0	00.0	00.0	•19.4	•	•03.3		
V3	81	•	•269	•094	•045	•000	•000	•000	•000	•050	•	•175	•088	•088	04.8	•68.8	39.0	00.0	00.0	00.0	00.0	•34.3	•	•05.6		
V4	81	•	•284	•101	•000	•012	•034	•000	•000	•055	•	•166	•018	•076	02.9	•10.8	00.0	01.2	14.5	00.0	00.0	•10.8	•	•03.5		
V5	78	•	•269	•076	•000	•046	•000	•000	•000	•030	•	•192	•072	•072	•03.0	18.0	00.0	23.0	00.0	00.0	00.0	16.5	•	•02.8		
V6	89	•	•235	•075	•000	•043	•000	•000	•000	•032	•	•159	•072	•072	•01.5	13.5	00.0	17.2	00.0	00.0	00.0	12.3	•	•01.7		

OVERALL INTERVALS			
QRS	P-R	Q-T	T P
•	•	•	•

VECTOR ANGLE VALUES			
QRS	T	P	QRST
052	114		053

ABNORMAL Q WAVE OR Q EQUIVALENT IN AVL
ALTHOUGH USUALLY NORMAL, OCCASIONALLY FOUND WITH LATERAL INFARCTION

J ELEVATED IN V3
ALTHOUGH USUALLY NORMAL, OCCASIONALLY FOUND WITH EARLY ANTEROSEPTAL INFARCTION

WIDE QS OR Q5 EQUIVALENT IN V1, V2, AND V3
ANTEROSEPTAL INFARCTION

AGE OF POSSIBLE INFARCTION IS INDETERMINATE

SMALL OR NEGATIVE T IN LEAD V5
SMALL OR NEGATIVE T IN LEAD V6
J DEPRESSION GREATER THAN 1 MM. IN 1 OR MORE LEADS
S-T AND T ABNORMALITIES

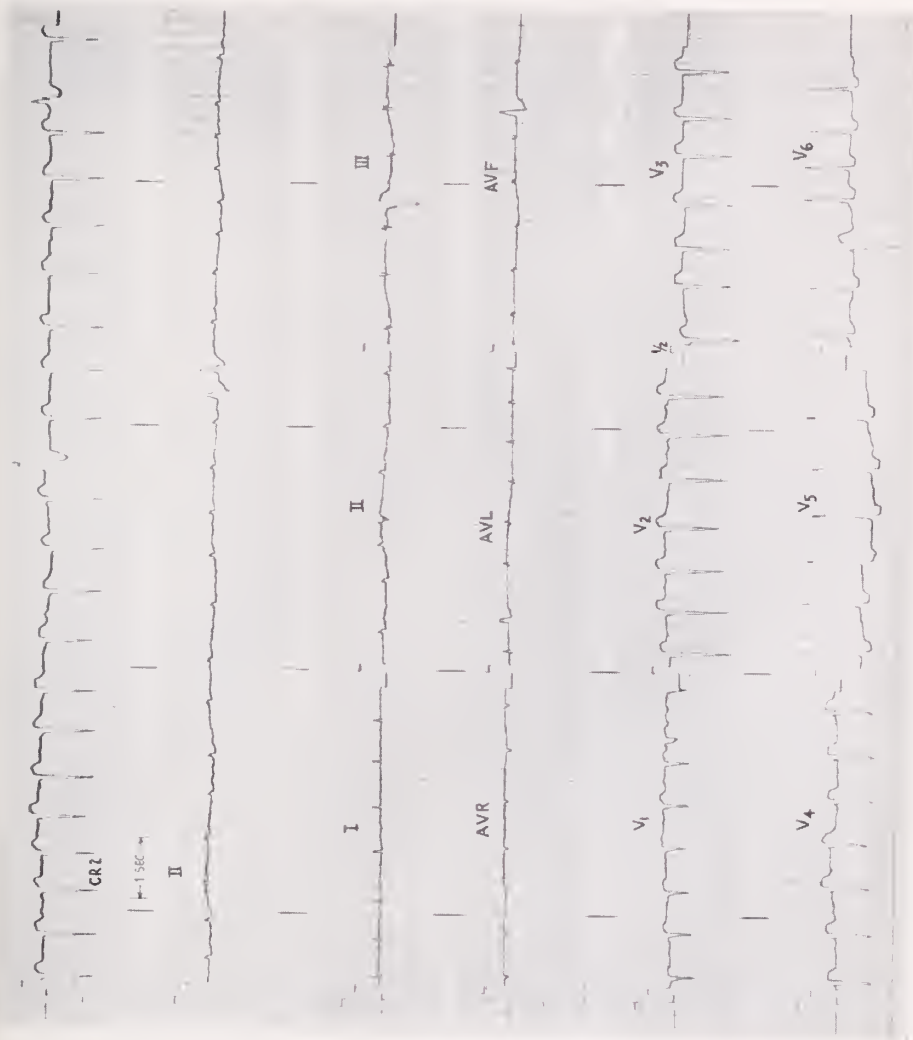


Fig. 6B. ECG Recording: Atrial Fibrillation, Ventricular Premature Systoles and Anterior Infarction.

MOUNTING ON CHART NUMBER 101101

MOUNT SINAI HOSPITAL IBM EXPERIMENTAL AUTOMATIC ECG INTERPRETATION

OCTOBER 14, 1966

THIS PRINTOUT IS FOR EXPERIMENTAL USE ONLY AND SHOULD NOT BE USED IN PLACE OF AN ECG INTERPRETATION BY A CARDIOLOGIST.

PATIENT NUMBER 055266 AGE 77 SEX FEMALE DRUGS NONE CLINICAL DIAGNOSIS ASHD

LCCATION 2000511 TECHNICIAN 2

•• RHYTHM ANALYSIS ••

THIRD DEGREE, COMPLETE, A-V BLOCK
THE ATRIAL RATE IS 94 PER MINUTE.

ECG MEASUREMENTS

LEAD NOS.	HR	P-R	Q-T	QRS	INTERVALS IN SECONDS					P	T	FWM	LWM	JJ	AMPLITUDE IN TENTHS OF A MILLIVOLT					P	T		
					I-Q	Q-R	R-S	S-RP	RP-SP						RJ	QRSTA	-C	R	-S			RP	-SP
I	45	.067	.505	.120	.000	.029	.041	.000	.000	.050	.055	.177	.045	.075	.00.8	.02.8	.00.0	.05.0	.04.9	.00.0	.01.4	.01.2	.02.4
II	44	.509	.131	.000	.032	.028	.000	.000	.071	.000	.032	.209	.039	.092	.00.9	.04.0	.00.0	.04.4	.10.5	.00.0	.00.0	.00.0	.05.7
III	45	.094	.487	.134	.000	.022	.030	.045	.015	.022	.062	.182	.026	.017	.00.4	.02.6	.00.0	.02.9	.14.2	.00.1	.00.2	.00.2	.00.8
AVR	43	.511	.185	.087	.048	.000	.000	.000	.000	.051	.000	.227	.102	.084	.00.7	.08.9	.04.3	.05.0	.00.0	.00.0	.00.0	.00.0	.00.1
AVL	46	.067	.602	.107	.008	.033	.042	.000	.000	.024	.057	.087	.010	.034	.00.1	.05.2	.00.4	.05.9	.01.5	.00.0	.00.0	.00.0	.00.7
AVF	47	.506	.130	.000	.029	.029	.000	.000	.073	.000	.066	.188	.034	.090	.00.4	.00.9	.00.0	.03.7	.12.0	.00.0	.00.0	.00.0	.00.6
V1	45	.558	.112	.014	.032	.000	.000	.000	.000	.066	.000	.199	.021	.089	.00.3	.11.0	.00.8	.05.3	.00.0	.00.0	.00.0	.00.0	.01.5
V2	46	.538	.136	.019	.031	.045	.000	.000	.041	.000	.041	.265	.021	.080	.00.6	.28.4	.02.8	.32.7	.04.2	.00.0	.00.0	.00.0	.05.2
V3	45	.113	.504	.127	.000	.030	.025	.000	.000	.072	.103	.222	.038	.087	.00.1	.05.9	.00.0	.05.3	.09.9	.00.0	.00.0	.00.0	.00.5
V4	44	.454	.132	.000	.033	.028	.000	.000	.072	.000	.072	.146	.041	.091	.00.0	.01.3	.00.0	.04.9	.09.6	.00.0	.00.0	.00.0	.00.7
V5	45	.112	.513	.133	.000	.030	.028	.000	.000	.074	.103	.205	.037	.089	.00.3	.02.2	.00.0	.03.9	.08.6	.00.0	.00.0	.00.0	.00.1
V6	45	.431	.125	.000	.028	.028	.000	.000	.069	.000	.069	.136	.035	.090	.00.6	.02.6	.00.0	.03.4	.08.2	.00.0	.00.0	.00.0	.02.6

OVERALL INTERVALS

HR	QRS	P-R	Q-T	T	P
45	.136	.091	.500	.199	.076

VECTOR ANGLE VALUES

QRS	T	P	QRST	J
-076	.061			-003

LEFT AXIS DEVIATION

ONSET OF INTRINSICOID DEFLECTION IS GREATER THAN .04 SEC. IN V1 OR V2

S IN I GREATER THAN .03 SEC.

QRS INTERVAL GREATER THAN .12 SEC.

RIGHT BUNDLE BRANCH BLOCK

QRS ANGLE BETWEEN -30 AND -90 DEGREES

SUGGESTS BILATERAL BUNDLE BRANCH BLOCK

T UPRIGHT BUT LESS THAN 7 MM IN V1

TALL R IN V1

SUGGESTS POSTERIOR INFARCTION

Q-T PROLONGED

Fig. 7A. Computer Printout: Complete Heart Block with Right Bundle Branch Block.

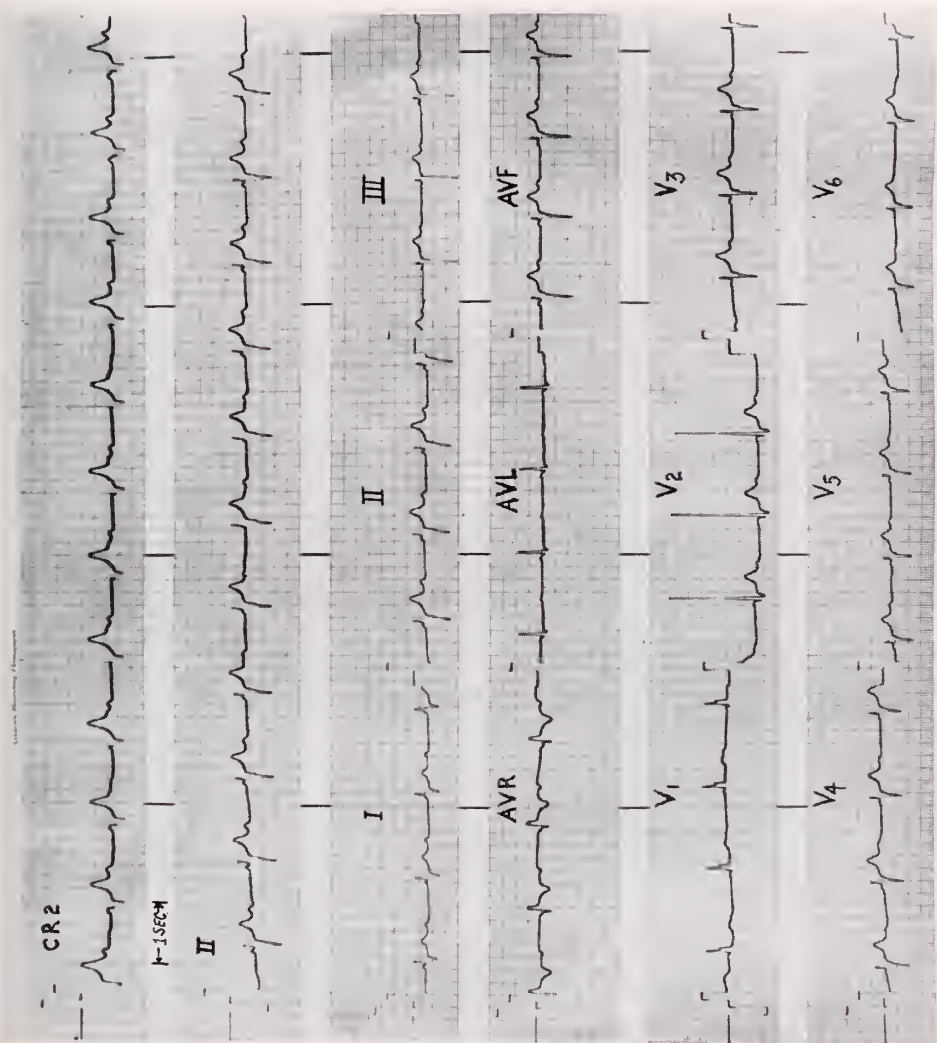


Fig. 7B. ECG Recording: Complete Heart Block with Right Bundle Branch Block.

MOUNTING ON CHART NUMBER 101010
MOUNT SINAI HOSPITAL IBM EXPERIMENTAL AUTOMATIC ECG INTERPRETATION

SEPTEMBER 1, 1966

THIS PRINTOUT IS FOR EXPERIMENTAL USE ONLY AND SHOULD NOT BE USED IN PLACE OF AN ECG INTERPRETATION BY A CARDIOLOGIST.

PATIENT NUMBER 270779 AGE 68 SEX FEMALE DRUGS CLINICAL DIAGNOSIS DIGITALIS HYPERTENSION •LVH•

TECHNICIAN
2
LCCATICA 2CCG355

•• RHYTHM ANALYSIS ••

SECOND DEGREE A-V BLOCK WITH THE WENCKEBACH PHENOMENON
THE ATRIAL RATE IS 75 PER MINUTE.

ECG MEASUREMENTS

LEAD NOS.	••	INTERVALS IN SECONDS										AMPLITUDE IN TENTHS OF A MILLIVOLT														
		HR	P-R	Q-T	QRS	I-Q	Q-R	R-S	S-RP	RP-SP	RJ	P	T	FWM	LWM	••	JJ	QRSTA	-C	R	-S	RP	-SP	GRSA	P	T
I	65	.264	.349	.074	.000	.036	.030	.000	.000	.007	.069	.179	.058	.014	00.0	03.1	00.0	08.9	00.6	00.0	00.0	00.0	00.0	05.0	01.1	01.1
II	68	.314	.270	.065	.000	.032	.000	.000	.000	.033	.136	.198	.057	.037	-00.4	04.3	00.0	13.1	00.0	00.0	00.0	00.0	00.0	07.4	01.4	01.6
III	65	.176	.357	.058	.000	.032	.000	.000	.000	.026	.096	.175	.058	.058	00.1	05.4	00.0	06.1	00.0	00.0	00.0	00.0	00.0	03.5	00.7	01.1
AVR	76	.251	.292	.075	.033	.000	.000	.000	.000	.042	.121	.199	.056	.056	00.4	-03.7	10.8	00.0	00.0	00.0	00.0	00.0	00.0	-06.0	-01.0	01.2
AVL	72	.141	.060	.000	.035	.000	.000	.000	.000	.025	.070	.060	.060	.060	00.3	02.2	00.0	03.1	00.0	00.0	00.0	00.0	00.0	01.8	.00	00.6
AVF	61	.243	.304	.069	.000	.034	.000	.000	.000	.035	.097	.238	.066	.066	-00.2	02.6	00.0	05.7	00.0	00.0	00.0	00.0	00.0	06.4	01.2	01.6
V1	76	.331	.274	.071	.000	.013	.034	.000	.000	.024	.099	.202	.016	.054	00.2	-07.8	00.0	01.4	17.8	00.0	00.0	00.0	00.0	-09.2	-00.3	00.7
V2	76	.339	.291	.089	.000	.018	.038	.027	.000	.007	.129	.106	.024	.014	00.3	-06.6	00.0	02.4	12.6	00.0	00.0	00.0	00.0	-05.7	01.3	00.9
V3	62	.314	.308	.086	.000	.037	.017	.027	.000	.006	.071	.154	.040	.015	00.3	-03.8	00.0	03.2	11.3	00.7	00.0	00.0	00.0	-02.2	00.7	-01.1
V4	63	.270	.303	.086	.000	.036	.018	.000	.000	.032	.113	.208	.051	.035	-00.2	05.0	00.0	02.0	02.9	00.0	00.0	00.0	00.0	05.1	00.8	-02.0
V5	78	.319	.277	.076	.000	.032	.000	.000	.000	.044	.090	.199	.075	.075	00.1	07.4	00.0	14.1	00.0	00.0	00.0	00.0	00.0	10.5	00.5	-01.6
V6	67	.255	.278	.075	.000	.032	.000	.000	.000	.043	.085	.192	.075	.075	00.0	06.2	00.0	11.8	00.0	00.0	00.0	00.0	00.0	08.8	00.5	-01.4

OVERALL INTERVALS

HR QRS P-R Q-T T P
69 .076 .280 .289 .179 .101

VECTOR ANGLE VALUES

QRS T P QRST J
05C -122 064 C49

P-R PROLONGED

QRS-T ANGLE GREATER THAN 120 DEG.

Q-T INTERVAL ABNORMALLY SHORT

SMALL OR NEGATIVE T IN LEAD II

SMALL OR NEGATIVE T IN LEAD V3

SMALL OR NEGATIVE T IN LEAD V4

SMALL OR NEGATIVE T IN LEAD V5

SMALL OR NEGATIVE T IN LEAD V6

T ABNORMALITIES, POSSIBLY CAUSED BY DIGITALIS

FIG. 8A. Computer Printout; Wenckebach Periods with Digitalis Intoxication.

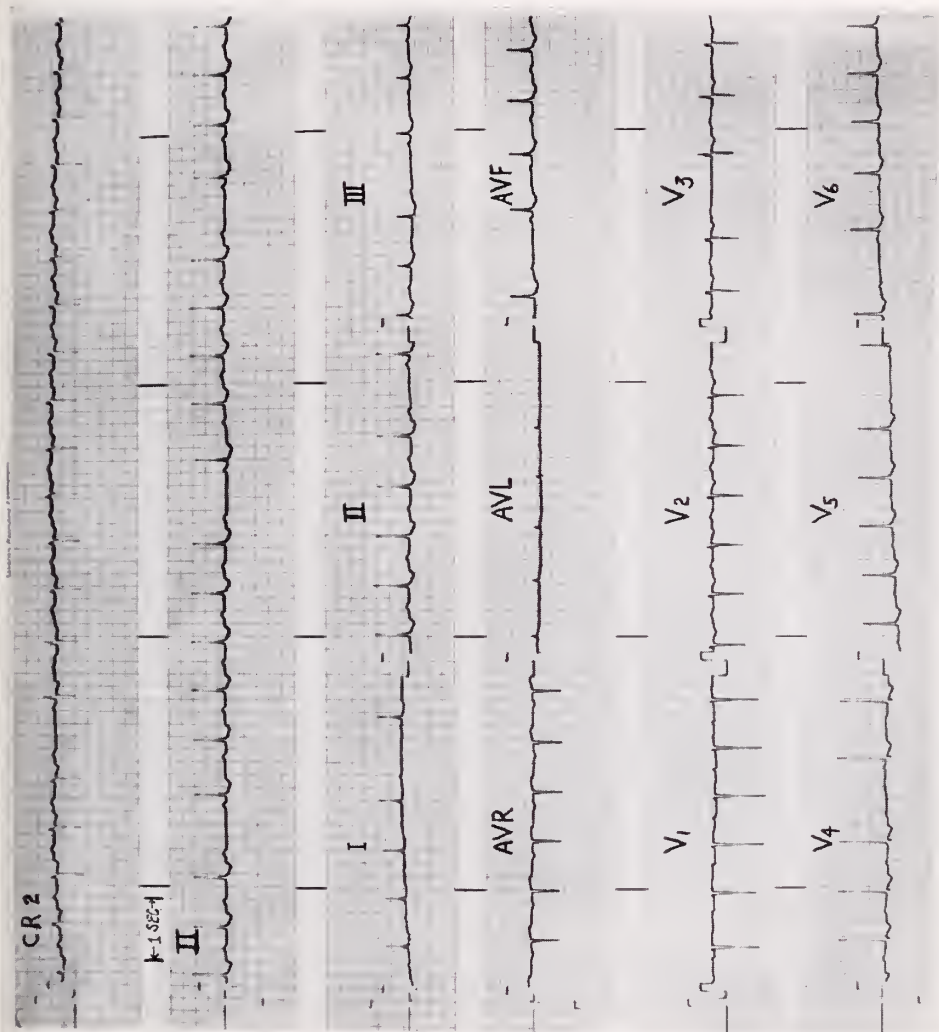
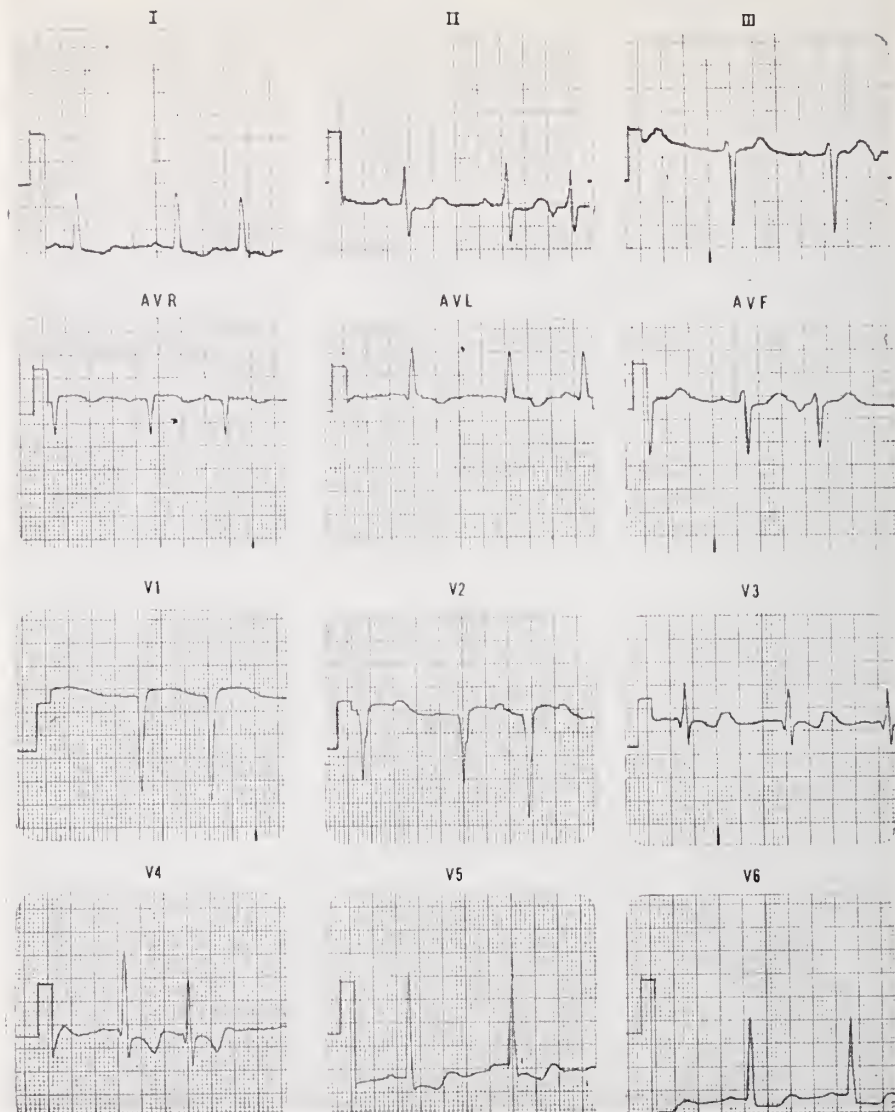


Fig. 8B. ECG Recording: Wenckebach Periods with Digitalis Intoxication.

MOUNT SINAI HOSPITAL - IBM COMPUTER PROCESSED ELECTROCARDIOGRAM



NAME MALE 75 UNIT NO. 338100 DATE 8/23/66 LOCATION GP 366 MOUNTING 001011 DRUGS: NONE; CLINICAL DIAGNOSIS: UREMIA AND/OR ELECTROLYTE DISTURBANCE. PROCESS VIA TELEPHONE

SINUS ARRHYTHMIA WITH VENTRICULAR PREMATURE SYSTOLES AND ATRIAL PREMATURE SYSTOLES WITH OCCASIONAL ABERRANT CONDUCTION.

LEFT AXIS DEVIATION (-33 DEGREES)

QS IN V1 AND V2; ABNORMAL Q WAVE IN V3; COMPATIBLE WITH ANTERO-SEPTAL INFARCTION; AGE OF POSSIBLE INFARCTION IS INDETERMINATE.

QRS INTERVAL .117 SEC.; INTRAVENTRICULAR CONDUCTION DISTURBANCE

J DEPRESSION IN I, II, AVL AND V4-6; NEGATIVE T IN LEAD I, AVL, V4 AND V5; QRS OF HIGH VOLTAGE; COMPATIBLE WITH LEFT VENTRICULAR HYPERTROPHY.

Q-T PROLONGED WITH LOW OR INVERTED T WAVES; COMPATIBLE WITH ELECTROLYTE IMBALANCE; SUGGESTS HYPOKALCEMIA.

Automatic ECG Interpretation: LEON PORGY, M.D.; CHARLES K. FRIEDBERG, M.D., Cardiologist

plete heart block (Figures 7A, and 7B) as diagnosed in the rhythm analysis section of the computer printout. The ECG parameter diagnostic statements include the abnormal left axis deviation (-76 degrees) and right bundle branch block which together suggest bilateral bundle branch block. Note the stated criteria for the computer diagnosis of right bundle branch block (Figure 7A). A further statement *suggesting* true posterior wall infarction was based on the tall R wave in lead V_1 in the absence of a tall T wave in this lead, which when present confirms this diagnosis. The criteria for true posterior infarction require further study. Finally, Q—T prolongation was noted.

The patient referred to in figure 8A is a 68 year old hypertensive woman receiving digitalis. The rhythm analysis discloses second degree A-V block with Wenckebach phenomenon. The rhythm statements concerning Wenckebach periods are correct. The various abnormalities detected in the ECG measurement section, including P—R prolonged, Q—T short as well as T changes, are grouped together to indicate the possible (and more likely, probable) relationship to digitalis intoxication. This serves to illustrate the advantage of relating the logic of the final diagnostic statements to the drug and clinical diagnosis of the particular case.

The final illustration (Figure 9) depicts the "mounted" computer processed electrocardiogram masked for delivery to the hospital chart. The case refers to a 75 year-old man with clinical diagnosis of severe uremia; the tracing was processed via telephone and the computer rhythm analysis and diagnostic statements were appended to the same sheet without the actual parameter measurements which are retained on the original printout. The presence of ventricular and atrial premature systoles (with occasional aberrant conduction) was noted as well as the abnormal left axis deviation, anteroseptal infarction, intraventricular conduction disturbance, left ventricular hypertrophy and suggestion of hypopotassemia.

DATA STORAGE

Following the computer printout, the measurements are stored on an IBM 1311 magnetic disc storage unit under the patient's hospital number for later retrieval for purposes of comparison. Simultaneous file storage of these data on cards allows for retrieval of cases which overflow the disc storage capacity and also for various other research projects. The final computer printout will state "no previous record available for comparison" if search of the disc does not reveal a matching patient's hospital unit number. Actually, three previous records are stored on disc in each case; if a fourth record is processed on the same case, the oldest record is removed from disc and retained on punch cards, leaving the latest three in storage. The record of both the 12 lead ECG and computer diagnostic statements is then available for distribution to the hospital chart and/or physician. After completion of the computer printout and data storage, the

Fig. 9. Computer Processed Electrocardiogram Mounted with Interpretation for Hospital Chart. The record refers to a 75 year old male with a clinical diagnosis of severe uremia.

entire cycle is then repeated automatically for the next case to be analysed and the process is then continuous.

In the present project, over 2,200 ECG tracings have been recorded by the technique described and processed by the computer. Periodically, formal detailed comparison has been made between computer printout and interpretation by the assigned cardiologists. The existing program is experimental; it has not been perfected, but is being continually altered as suggested by the feasibility testing. A survey of the first 154 cases made June, 1966 showed that of 344 pertinent diagnostic statements in this group 317 were printed and 40 of these were considered to be incorrect. The first 2,000 recorded cases are being studied in detail at present for determination of the specific degree of accuracy, which appears to be approximately 90 per cent.

As a by-product of this work, previously accepted measurement parameters have been challenged and altered to meet the findings. For example, the accepted criteria for low voltage of electrocardiograms were found to include such a vast number of normal subjects that we were forced to amend the logic for more accurate delineation. Furthermore, computer statistical methods will be utilized with the disc stored parameter ECG measurements for improvement of our diagnostic criteria.

DISCUSSION

The approach presented offers a complete system for routine ECG analysis including rhythm as well as parameter measurement and anatomical diagnosis. The "mounting" function of the 12 leads by computer eliminates technician error and frees the technician for other work just as the automatic analysis relieves the electrocardiographer for other duties.

The method of testing at present includes interpretation of the strip chart tracings by three cardiologists and recording of their results on a special form (Figure 3). Later specific detailed comparison is made between the physician's interpretation and the computer analysis for this feasibility study.

Stimulated by the availability of appropriate equipment as well as the subjective nature of measurement of customary cardiographic tracings, increasing numbers of investigations have been assayed on the application of computer methods in the field of cardiology, and specifically, electrocardiography. The application of computer analysis in electrocardiography has been developed to a high degree, but the field remains sharply divided into two opposing schools; one favoring *electrocardiographic* and the other *vectorcardiographic* analysis. Pipberger et al (9, 10) have presented the automatic analysis utilizing the Frank corrected orthogonal vector lead system. Their presentation of criteria for normal measurements for the Frank vectorcardiogram should prove valuable. On over 50,000 Frank vectors analyzed automatically by digital computer at the Mayo Clinic, Smith and Hyde (11) have reported good correlation with the electrocardiographic interpretation by their reporting cardiologists.

In contrast to the workers utilizing *vectorcardiograms*, Caceres (6) has

championed analysis of the *electrocardiogram* for routine use. He is proposing a central pooling of all data in order to establish uniform national criteria for computer ECG analysis. In this regard, we agree that for general acceptance at present, it is preferable to utilize the customary 12 lead electrocardiogram for digital computer analysis. However, simultaneous utilization of both methods of computer analysis in the same cases will provide concrete information in the future as to the relative differential diagnostic value of each.

SUMMARY AND CONCLUSION

A joint Mount Sinai Hospital—IBM study project has been undertaken to determine the feasibility of an experimental hospital oriented digital-computer program for analysis of the electrocardiogram. The program as developed to this stage presents a fully automatic and fairly reliable system for this purpose. The sources of errors revolve primarily about preciseness of wave measurement, rather than the “rhythm” or “diagnostic” logic. In general, parameter measurements by computer are slightly wider than those made visually by electrocardiographers since the points of departure of the waves from the baseline are detected less precisely by the clinicians.

The program simulates the functions of the electrocardiographer automatically; it provides analysis of the cardiac rate, rhythm and diagnosis of the electrocardiographic abnormalities; and it stores the measurements for comparative purposes. Observer variability and physician intuition are to be replaced by the uniformity of the machine, yet a vigorous attempt is made to retain the “art” of ECG interpretation within the diagnostic logic for the computer. The experimental program requires constant study and revision in order to obtain the highest possible degree of accuracy; the diagnostic logic for the comparative program is in preparation.

The value in simulating the functions of the electrocardiographer is that he may be freed for other, more vital tasks. Likewise, the provision of a printed diagnosis plus automatic mounting of the 12-lead electrocardiogram will enhance the productivity of the ECG technician.

The 1401 IBM computer system and the experimental ECG data gathering console and other peripheral equipment are described as well as the data flow, analysis and storage. Representative illustrative cases in normal and abnormal cardiac states and an example of a mounted tracing for the hospital chart are presented.

Thus, an overall practical experimental system for computer analysis of the electrocardiogram has been utilized for routine hospital work. It should be emphasized that the system and the program are still under development and are not available at this time. However, the system as developed will provide parameter measurements in data processing form, thereby enhancing its value in teaching and making feasible research efforts toward improving criteria for electrocardiography. It will enable us to establish more accurately the minimal diagnostic criteria necessary for the electrocardiogram in heart disease. Furthermore, application of the program for the improvement of ECG monitoring fa-

cilities as in coronary care units may well be one of the most significant contributions of the project. Although the system is hospital oriented, it may be applied to community health services (as in the new regional medical program), to screening purposes and finally, to routine office work by the local medical practitioner.

In conclusion, the experimental computer program, as described, ideally allows for general uniformity, accuracy, and reproducibility of ECG diagnosis. It is possible that the system could be available 24 hours a day via simple telephone transmission of the ECG signal. Utilization in large hospital centers may serve huge urban and suburban areas. It is hoped that such applications will be the eventual achievements of our attempt in this project to produce clinically acceptable results in computer analysis of the electrocardiogram.

Acknowledgment

We wish to express our indebtedness to Fran Griffith, Stanley Manning, Joseph Mastrangelo, Alan Barnes, Donald Wortzman, William Gilmore of IBM and Mrs. Gail Richards, Susan Gruff and Lee Wolf for their participation in technical aspects of this project. We wish also to thank Dr. Jacob Hirsch of N.Y.U. and Dr. Lloyd Fallowes of Mount Sinai Hospital for their aid.

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Announcements

THE RALPH COLP AWARD FOR 1966

Dr. Irwin M. Gelernt and Dr. Sigmund H. Ein are recipients of the Ralph Colp Award for 1966. The award is given for their report in *The Journal of The Mount Sinai Hospital* evaluating the immunosuppressive capacity of Alkeran.



This award is made by the Ralph Colp Fund, established by his colleagues and friends in honor of Dr. Ralph Colp and in recognition of his long years of distinguished service to The Mount Sinai Hospital and to American surgery.

THE DANIEL STATS MEMORIAL PRIZE FOR 1966

The Dr. Daniel Stats Memorial Committee is pleased to announce Dr. Klaus Dittmar of the Department of Hematology, The Mount Sinai Hospital, New York, N. Y. recipient of the Daniel Stats Memorial Prize for 1966. His paper titled "Coexistence of Polycythemia Vera and Biclonal Gammopathy (γ GK and γ AL) with Two Bence Jones Proteins (BJK and BJL)" and written with Dr. Shaul Kochwa, Dr. Dorothea Zucker-Franklin, and Dr. Louis R. Wasserman, was presented in part at the Eighth Annual Meeting of the American Society of Hematology, December 1965. Dr. Dittmar received his M.D. degree from Medizinische Fakultät der Universität Heidelberg.

By terms of the Fund, the award is granted to a member of the House Staff who during the current academic year has published or has accepted for publication, the most meritorious paper on a subject with hematologic orientation. It is the hope of the Committee that subsequent awards will equal the high quality of this year's selection.

Alan F. Guttmacher, M.D., Chairman
Alexander B. Gutman, M.D.
Lester R. Tuchman, M.D.
Louis R. Wasserman, M.D.

The Teaching Hospital Experience

S. B. GUSBERG, M.D.

In the search for a graceful formula to indicate my ceremonial thoughts on retirement from this office, I am deeply aware of the great honor you have bestowed upon me with the Presidency of our Society and humbled by this designation in its Centennial year. I am further moved by the somber consideration that I must make this presentation without lantern slides. To any physician who has been a teacher, such a cruel challenge seems an indecent exposure but I hope that I may expect as compensation your tolerance with my public utterance of some private thoughts about our profession and our discipline.

I wish first to express my gratitude to the members of the Council, its Officers, its Program Committee, its Historian and especially, its Secretary, who have worked so hard, so enthusiastically and energetically to support the program of our Centennial year, but deep as is my debt to my friends, I cannot burden them with responsibility for the acts of my tenure. In this respect I can only emulate Sir Thomas More on the occasion of his execution: approaching the steps to the scaffold he asked the lieutenant to give him a hand going up, but quickly added, "coming down, I will shift for myself."

We are all concerned, in one way or another, with the teaching of medicine, indeed it is our sworn duty; but the lay public has also entered this area of concern through the communications media and the journals of public opinion that have taken an almost militant position about matters of public and personal health. Thus it may be of interest to attempt a definition of our function as teachers, and to appraise our public role. Of course, every good physician is a teacher in the sense of teaching preventive medicine and hygiene to his patients and translating for them the technical anti-language of scientific medicine. The great practitioner of medicine has this capacity in great measure for he has empathy for the patient who, anxious and insecure, is already experiencing a diminution in his personal status as a result of poor health. The practitioner offers this patient respect for his dignity and equanimity, considers him as an individual rather than a disease entity, and treats according to the patient's ego needs rather than his own. His task in this interpersonal relationship is to support the patient by understanding the psycho-emotional context of the patient's physical disease and naturally, then by offering his advice without pomp or rigidity, think-

From the Department of Obstetrics and Gynecology, The Mount Sinai Hospital and Columbia University.

Presidential Address read before the New York Obstetrical Society, May 21, 1963. Reprinted in part from American Journal of Obstetrics and Gynecology 87: 848, 1963, C. V. Mosby Co., St. Louis, Mo.

only of the patient's needs. Of course, the physician requires some consideration of *his* position in this relationship as well, for his role has been made difficult in an era where the mystique of medicine has been diluted by the widespread do-it-yourself gospel. We sympathize with the obstetrician who expressed his opinion of natural childbirth by paraphrasing the late Alexander Woolcott's view that in modern society the two oldest professions had been ruined by amateurs.

One can narrow the definition of medical teaching to a consideration of the educational programs of all hospitals where house officers and nurses are taught, but it might help us focus on the teaching problems of the present day by narrowing our range even further to the educational problems of the teaching hospital. Here undergraduate or graduate courses are given and a balance of patient care, teaching and research is sought. The primary relationship that bears inspection here is the encounter of the practising clinician and the full-time teacher and investigator. This relationship which is crucial to the development of a teaching program has become filled with tension and even hostility by an artificial separation of these two groups, each of which, by a somewhat different approach perhaps, seeks the same goal: the application of medical science to the care of the sick. In medicine's search for a balance between humanistic empathy and scientific progress, artificial tensions have been created by those who imagine a conflict between science and the humanities. This is a concern that is not confined to the physician but is worldwide. As the late Mr. A. Whitney Griswold, recent President of Yale University has said: "In each generation we renew man's immemorial effort to find his place as an individual in a world that seems to recognize him only as a species."

Sometimes the schism between practicing physicians and teaching physicians caricatures the image of the full-time doctor who arrives at the hospital in his Volkswagen, his crew-cut bristling in the *late* morning sun, jauntily bow-tied, casually sport-coated to take up his small physicianly and large administrative duties. There is a profile etched with some acidity on the other side of the coin too that characterizes the elegant clinician as one with any time he can spare from his personal adornment spent on the neglect of his patients. The full-time teacher, sometimes imbued with the material sacrifice that he has made for his ideal of scientific medicine, may expect advancement without accomplishment; while the part time clinician-teacher eyes the full-timer suspiciously, willing to have him play a super-resident role, performing the necessary and sometimes harassing administrative duties that will make an efficient unit for treating private patients, but expecting him to carefully refrain from the treatment of patients which, in any case, he expects him to do shabbily. In actuality the responsibilities of these two groups are complementary, not competitive. No teaching unit is complete without the effective contribution that each can make. We must remember that full-time teaching status should not remove a physician from his profession, for clinical virtuosity must be the final hallmark of distinction in clinical medicine and no quantity of publication can restore the respect of colleagues and students which a teacher has lost by separation from the "performing art" he has been designated to teach. The teaching of a clinical craft by non-

practitioners will always be a graceless, inefficient ritual without the sparkle and authority that the ultimate responsibility inherent in patient care can confer. Just so must there be opportunity for both categories of teachers to participate in research, though it is clear that the full-time teaching physician will play the major role here more often by virtue of his freedom from full private practice responsibility and greater opportunity for the acquisition of basic laboratory skills. In the teaching of students, again, both should participate, according to their interest and skill; it is in this sector, that the practicing clinician can make his special contribution for he is steeped in the daily concern for the patient's personal welfare.

It is alleged that the care of patients by the physician in the teaching hospital is characterized by greater time spent with the patient and family, personal pre-operative and postoperative care, careful explanation of technical procedures to the patient and deeper understanding of the laboratory language and data. But here we are only defining professional and personal honesty, compassion and competence, and these are qualities common to all distinguished clinicians. The pursuit of excellence makes a clinician great in just the same measure that it makes a hospital or teaching institution great.

I must pause here to recapitulate my view that the order of priority for the activities of the teaching hospital must be patient care first, teaching second and research third, but I do not believe that emphasis in any of these spheres requires the neglect of the others. Cynics point to patient care in these institutions as the prime responsibility of physicians in training, (the resident physicians who are perhaps as yet something short of polished clinicians) and there has been widespread concern with the lack of reward for virtuosity in teaching in an era when public support for research is so great that quantity of publication and scientism appear prominently in the fiscal framework that holds some institutions of higher learning together.

And yet we know that in these teaching institutions there are men who have found, in some way, the unique qualities that have inspired their colleagues and students to excellence. We know that the presence of students, undergraduate or graduate, elicits a kind of warmth and interest and, perhaps I may be permitted to use the word, humanity, in a hospital, that enriches this service immeasurably and increases in just that amount its contribution to the community and to the profession. We know that in these same institutions medicine must advance by scientific research and that the complexity of scientific medicine has become so great that teamwork between clinician and basic scientist is required—dabbles into chemistry and physics will not suffice to advance knowledge even by the most highly motivated physicians. I do not concur here with the easy philosophy that clinical abilities and research abilities cannot reside in one individual, nor yet am I seeking the renaissance man of so many multifaceted talents that Oliver Wendell Holmes spoke of him with admiration as occupying not a chair in the University, but a settee. I do submit that contributions to all phases of these needs of the teaching hospital may be made by gifted, interested and energetic individuals without sacrifice of their truly physicianly role. In some small meas-

ure I concur with the Dean of a famous medical school who told me recently that one mission of a great teaching center is to save obstetrics and gynecology from its own technical virtuosity. This integration of needs was expressed well by the Boston physician who said that it "was our duty to gain all the knowledge possible to improve our ability to heal the ills of our patients. Sympathy is not enough in the face of scientific ignorance, any more than science can wipe away the grief of a bereaved parent."

With respect to the organizational and administrative aspects of the teaching hospital life upon which the label "politics" is so often misplaced, I can only say that human affairs and politics in this sense go hand in hand without any possibility of separation. Mature and reasonable men know that the interplay of personalities in constructive manner requires committees and compromise, tables of organization and secretarial protocol, and some other trappings of organization that are frequently anathema to the independent spirit of the physician.

With the maturation of our own discipline it has assumed an even more important role in the hospital, the medical school, and the community: we are obliged to ask not what are our privileges, but what are our duties in the social structure of modern life. Our public image and usefulness must no longer suffer by deviation from the Hippocratic spirit, unless we wish our profession to share in the new era of me-too trade unionism. It would be nice for someone to mention publicly that there are still some physicians who have never gotten over the wonder of being paid for work that is fascinating, natural and necessary for them, who are both honest and competent in the care of the sick.

I wish to offer the view that the discipline of obstetrics and gynecology will lead the way for other specialties in the teaching hospital organization of the future, because of its fusion of medical and surgical techniques and attitudes, its heavy emphasis upon preventive medicine and social values, and its deep consideration of the psycho-emotional context of physical disease. It would appear that all regional specialties must move in this direction as the purely technical consideration of the surgical approach gives way to advancing knowledge of the physiological, psychological, endocrine, and metabolic aspects of diagnosis and treatment of disease. The obstetrician-gynecologist now deals with problems of his patient's adolescence, reproductive life and advancing age by utilizing the techniques of medicine, surgery, endocrinology, psychiatry, radiotherapy and pathology, to name a few. He brings a skilled but broad basic approach to the problems of his patient's reproductive function. Even in the highly technical areas of cardiac and thoracic surgery the surgeon must utilize the physiological approach of the internist and surely understands the diagnostic problems of his surgical region as well as they. It would appear that the surgical specialist of the future will spend as much time preparing himself for the deep understanding of the biology of his regional diseases as he will in the perfection of his surgical procedure. I do not plead here for technical incompetence, but ask only for a reassessment of the role of the adjuvant disciplines in other surgical areas that our specialty has already encompassed.

In closing I must note that our profession has become increasingly scientific and complex and I can understand the impatience with which the Nobel Laureate, Szent-Gyorgi, replied to the young man who expressed the wish to go into science in order to help people: "Go into philanthropy, young man," he said, "it's easier." And yet in the quest for excellence in our profession and in our teaching hospitals I must agree with the recent President of the American College of Obstetricians and Gynecologists, Dr. Edward Hughes: to you gentlemen—Noblesse oblige; it is the duty of those with superior education and training to restore to their profession a measure of what they have taken from it; to contribute to their hospital by teaching or research, a standard of unswerving clarity that will be example to those who follow us.

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The Effect of Probenecid On Serum Lipids: A Study of Diabetics and Non-Diabetics Without Gout

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Recent investigations have been concerned with the interrelationship of disorders of lipid, carbohydrate, and uric acid metabolism and ischemic heart disease (IHD). Approximately 90% of subjects with IHD (1-3) have serum cholesterol >260 mg/100 cc and/or serum triglyceride concentration >150 mg/100 cc. Hypercholesterolemia of this magnitude has been described in 45 to 70% of this group and hypertriglyceridemia in 50 to 80% of this group. Similarly hypercholesterolemia and particularly hypertriglyceridemia have been noted in diabetes (4). A considerable proportion of subjects with hypertriglyceridemia are latent or overt diabetics (5, 6). Forty to sixty per cent of diabetics develop IHD and a comparable number of those with IHD manifest disturbance of carbohydrate metabolism (7-9). Hyperuricemia has frequently been noted in patients with IHD, and gout is often complicated by coronary artery disease (10, 11). In both gouty and non-gouty subjects, hyperuricemia and hypertriglyceridemia are frequently associated: hyperuricemia and hypercholesterolemia are less closely related (12, 13). A diabetic response has been demonstrated in 60% of subjects with gout (14). High caloric, high fat diets rich in saturated fatty acids have been associated with IHD, diabetes, hyperlipidemia, and gout (2, 15). A rise in serum lipids and uric acid levels occurs from youth to middle age in groups consuming such a diet (11). These conditions are uncommon in populations habituated to a low caloric, low fat diet rich in unsaturated fatty acids (2).

With the elucidation of these relationships, increasing interest has focused upon drugs which influence carbohydrate, lipid, and uric acid metabolism. Probenecid, a potent uricosuric agent, is effective in lowering elevated serum uric acid levels and in mobilizing tophaceous deposits in gouty subjects (16, 17). This investigation was undertaken to ascertain the effect of probenecid on serum cholesterol, triglyceride and uric acid levels and blood sugar in diabetics and non-diabetics without gout.

MATERIAL AND METHODS

Forty subjects were selected from the outpatient clinics of the Elmhurst Hospital Division of the Mount Sinai Hospital, New York. They included 13 non-diabetic men, 9 non-diabetic women, 11 diabetic men and 7 diabetic women. The mean ages of these groups were 53, 58, 63, and 55 years respectively. None had thyroid disease, gout or significant gastrointestinal disease. Agents known to

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alter uric acid or lipid metabolism were withheld during the course of the investigation. Diabetic subjects were maintained on a constant dose of tolbutamide and a modified low carbohydrate diet.

Probenecid was administered in a dose of 0.5 gram four times daily for a period of 8 weeks. Blood samples were drawn before the start of probenecid, at 2 weeks, 4 weeks, 8 weeks, and at 12 weeks (4 weeks after probenecid was discontinued). All subjects were instructed to maintain a high fluid intake, and there were no instances of renal calculi during the study. Probenecid was discontinued in one subject because of a dermatitis which subsequently subsided. One diabetic male discontinued tolbutamide during the initial eight weeks of the investigation, but took probenecid as directed. This patient, and a female with mild diabetes and marked hypertriglyceridemia are considered separately.

Venous blood samples were drawn after a 12 hour patient overnight fast. Uric acid and blood glucose determinations were conducted at Elmhurst Hospital Clinical Chemistry Laboratory, and serum cholesterol and triglyceride determinations were conducted at the Nutrition Laboratory of the Mount Sinai Hospital (18-21). In analyzing the data, a $p < 0.05$ was considered statistically significant.

RESULTS

Uric Acid

Serum uric acid levels during the course of probenecid were considerably lower than the control values. These reductions were statistically significant in non-diabetic men and women and in diabetic men at two and four weeks and in diabetic women and eight weeks after the start of probenecid. Mean serum uric acid levels at 12 weeks (4 weeks after probenecid was discontinued) were 0.4 to 1.3 mg/100 cc higher than initial control levels. The 12 week mean uric acid concentration in non-diabetic women was significantly higher than the control value in this group (Fig 1).

Thirty-two percent of subjects had a 12 week level 25% or more above the control uric acid concentration. Ten percent had a 12 week level 25% lower than the control value. Serum creatinine was measured in nine subjects who experienced a "rebound" rise in uric acid and in six subjects who did not manifest such rise. Significant drop in uric acid concentration occurred in both of these groups during probenecid administration. The serum creatinine, however, remained within normal limits in both groups (Fig 2).

Fasting Blood Sugar

Probenecid did not significantly alter mean blood sugar levels in the four groups studied. The somewhat lower levels noted in diabetic subjects during the entire course of the investigation may be related to the frequency of clinic visits and subsequent closer adherence to the diabetic regimen previously prescribed (Fig 1).

Serum Cholesterol

During probenecid administration there were no significant changes in serum cholesterol (Fig 1). Fifteen subjects with an initial cholesterol 260 mg/100 cc were analyzed separately. Probenecid significantly lowered uric acid levels in these subjects, but did not influence cholesterol (Fig 2).

PROBENECID, BLOOD SUGAR, SERUM CHOLESTEROL, TRIGLYCERIDE AND URIC ACID LEVELS

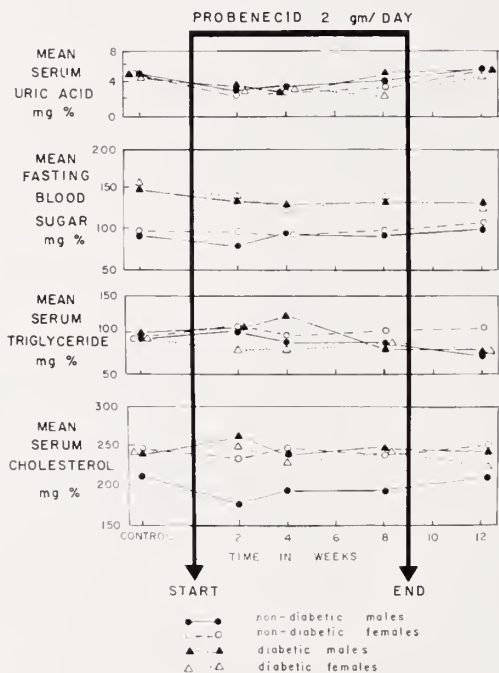


FIG. 1.

Serum Triglycerides

There were no significant differences in serum triglyceride levels during the course of Probenecid (Fig 1). Eight subjects with an initial serum triglyceride > 140 mg/100 cc experienced a significant fall in uric acid but no change in mean triglycerides (Fig 2).

Additional Data

A 55 year old diabetic man failed to take his usual hypoglycemic therapy, tolbutamide, during the eight week course of probenecid. Fasting blood sugar rose from an initial level of 232 mg/100 cc to 400 mg/100 cc, cholesterol from 344 to 353 mg/100 cc and triglycerides from 350 to 400 mg/100 cc. Uric acid fell from

an initial level of 6.7 to 2.4 mg/100 cc during the administration of probenecid. At eight weeks, probenecid was discontinued and tolbutamide resumed. Four weeks later the blood sugar was 182 mg/100 cc, cholesterol 283 mg/100 cc, triglycerides 127 mg/100 cc, and uric acid 4.9 mg/100 cc.

A 65 year old diabetic woman with marked hypertriglyceridemia, experienced no change in blood sugar levels or serum cholesterol during probenecid. Uric acid fell from 5.9 to 3.7 mg/100 cc and rose to 5.5 mg/100 cc four weeks after probenecid was discontinued. The serum triglyceride concentration was 405 mg/100 cc initially, 380 mg/100 cc at two weeks, 718 mg/100 cc at four weeks, 703 mg/100 cc at eight weeks, and 700 mg/100 cc four weeks after probenecid was discontinued.

METABOLIC EFFECTS OF PROBENECID 2 gms. PER DAY FOR 8 WEEKS

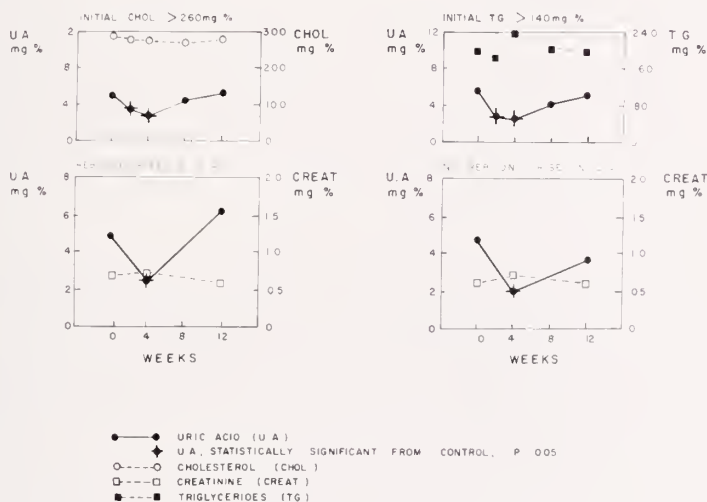


FIG. 2.

DISCUSSION

Hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and hyperglycemia, commonly associated metabolic abnormalities in gout, ischemic heart disease, and diabetes, are currently believed to be genetically determined, but may be profoundly influenced by drugs and diet. For this reason a study was undertaken to evaluate the effects of probenecid, a potent uricosuric agent, on lipid and carbohydrate metabolism.

The administration of probenecid, 2 grams daily for 8 weeks, produced a significant drop in serum uric acid in diabetic and non-diabetic subjects without gout. This was observed in subjects with hypercholesterolemia (a control cholesterol > 260 mg/100 cc and in subjects with hypertriglyceridemia (initial triglyceride > 140 mg/100 cc. A rebound rise in uric acid (25% or greater than the control level) occurred in 32% of subjects four weeks after probenecid was dis-

continued. This rise in uric acid was not related to impairment of renal function as the serum creatinine concentration remained within normal limits in both subjects who experienced a rebound rise in uric acid and in those who did not. A rebound rise in uric acid might be explained by increased uric acid synthesis during the period of probenecid. Crone and Lassen have presented presumptive evidence of increased uric acid synthesis in 7 of 15 normal subjects receiving probenecid (22). According to an oral communication from T. F. Yu, M.D., in 1966, the rise in uric acid concentration after probenecid was stopped may be attributed to over compensation of homeostatic mechanisms regulating the uric acid pool analogous to the rebound hyperglycemia observed after hypoglycemia or to the hypercoagulable state noted after anticoagulant drugs have been abruptly discontinued.

The results of the present study showed that probenecid did not influence blood glucose, serum cholesterol, or triglyceride levels in non-diabetic and diabetic subjects without gout. These results are in agreement with a short-term investigation by Edelman et al who administered 1.5 gram probenecid daily for 2 to 3 weeks to 10 patients with myocardial infarction (23). No significant alterations in serum cholesterol, triglycerides, lipid phosphorus, or I 131 triolein clearance occurred during probenecid therapy, although appreciable falls in serum uric acid were observed in each patient. One patient, with an initially high serum triglyceride level, experienced a rise in triglycerides, similar to that noted in our subject, W.E.

Thus, despite the close interrelationship of disorders of lipid carbohydrate and uric acid metabolism, an agent which lowers uric acid levels by inhibiting tubular reabsorption of uric acid need not necessarily lower serum lipid and blood glucose levels. Conversely, Kershbaum et al have demonstrated that pyrazinamide, an antituberculous agent, which raises serum uric acid levels by suppression of tubular excretion of uric acid, does not cause a concomittant rise in serum cholesterol, phospholipid, and lipoprotein levels (24).

Several agents do influence uric acid at a tubular level and in addition influence carbohydrate and lipid metabolism through other mechanisms. The benzothiadiazine compounds elevate serum uric acid by suppression of tubular urate excretion and increase blood sugar concentration in both diabetics and non-diabetics (25). Changes in carbohydrate tolerance have been related to a decrease in assayable serum insulin and an alteration in tissue glucose metabolism (26, 27) or both. Diazoxide, a nondiuretic benzothiadiazine, has been reported to increase plasma free fatty acid levels (28). Acetohexamide, an oral hypoglycemia agent, may lower serum uric acid by blocking tubular urate reabsorption (17).

Diet profoundly influences carbohydrate, lipid, and uric acid metabolism. The beneficial effects of low carbohydrate diet in diabetes, low purine diet in gout, and low caloric, low fat diet rich in unsaturated fatty acids in hyperlipidemia have been documented (2, 4, 15, 16). A high fat diet has been reported to raise uric acid by interfering with the tubular excretion of uric acid (29).

Hyperlipidemia, hyperglycemia, and hyperuricemia may be modified by ap-

propriate drug and dietary therapy. Hopefully correction of these biochemical abnormalities may reduce the present high morbidity of IHD, diabetes and gout.

SUMMARY

The administration of 2 gram of probenecid daily for eight weeks produced significant fall in serum uric acid level, but no significant changes in serum cholesterol and triglycerides and blood sugar in 40 diabetic and non-diabetic subjects without gout. These results were observed in both hypercholesterolemia and hypertriglyceridemic subjects.

A rebound rise in uric acid concentration (25% higher than the control level) occurred in 32% of subjects four weeks after probenecid was discontinued. This was not associated with changes in serum creatinine concentration and was attributed to an "overshoot" of homeostatic mechanisms controlling the body uric acid pool.

Certain drugs such as probenecid and pyrazinamide influence tubular processing of uric acid, but have no effect on lipid or carbohydrate metabolism. Other compounds such as the benzothiadiazine diuretics and acetohexamide influence uric acid at a tubular site and carbohydrate and/or lipid metabolism through other distinct metabolic pathways. The relationship of diet to carbohydrate, lipid, and uric acid metabolism is briefly reviewed.

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Surgery of The Hand in Rheumatoid Arthritis

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Although the clinician may be interested in the etiology, biochemistry, genetics and natural history of the disease, the patient with rheumatoid arthritis perceives of his disability as neither an example of disordered globulins nor of immunological response. He is afflicted with painful abnormal joints which operate in an abnormal fashion, and for which he seeks relief. There has long been a mistaken impression that surgical measures to relieve such problems should be reserved exclusively for the treatment of the severe "burned-out" rheumatoid cripple with hopelessly irretrievable deformities. It is our belief that surgical treatment is a significant contribution to the total care of the rheumatoid arthritic. An increasingly large number of orthopaedic surgeons and rheumatologists throughout the world support this view.

The objectives of rheumatoid surgery are: relief of pain, prevention of destruction of cartilage or tendon, and the general improvement of joint function. The specific procedure may be directed toward soft tissue, tendon, bone, or the actual joint structures. From the surgical point of view there are two types of rheumatoid arthritis; "stiff" and "loose." The "stiff" type appears to involve the synovium of the joints often leading to ankylosis in unacceptable positions. The "loose" type is characterized by unstable joints and appears to involve primarily the synovium of the tendon sheaths about the joints with consequent tendon imbalance. The latter type is more common. Fortunately, this type also responds better to surgical measures.

Whatever the biological cause of rheumatoid arthritis on the molecular level is and however variable the clinical manifestations, it is the synovial tissue which appears to provide the "unique milieu" in which the rheumatoid chain of events occurs (1). This has given rise to the hope that prophylactic synovectomy of a prominently involved joint early in the clinical course of the disease may spare that joint future damage (2). Synovectomy is combined with other prophylactic and reconstructive procedures wherever feasible.

THE HAND

There is probably no area of the body where the effects of rheumatoid arthritis are as dramatically destructive as in the hands. Due to the complex interaction of muscle balance and joint motion required for normal hand function, a relatively minor degree of anatomic loss can cause a proportionally major degree of functional loss. Significant anatomical change can be totally disabling, converting the hands into crude claws.

The pathogenesis of rheumatoid deformities in the hand is similar to that in most other joints (3, 4). With inflammation there is synovial swelling and en-

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gorgement and subsequent stretching of joint capsules. As a result, beginning subluxation of the joint causes minor tendon imbalance. This perpetuates and increases the joint subluxation, often to the point of dislocation with the tendon imbalance increasing at the same rate as the joint instability. The discomfort and mechanical instability superimposed upon the pain and destruction of the rheumatoid arthritis itself yields a profound combined disability.

In general, four basic deformities are seen in the hand; ulnar drift at the metacarpophalangeal joints, "swans-neck" deformity of the finger, boutonniere deformity of the finger, and "flexion-hyperextension" deformity of the thumb.



FIG. 1. Marked ulnar drift of all fingers in a patient with rheumatoid arthritis of seven years duration.

ULNAR DRIFT

Ulnar drift, the term used to describe the classical subluxation of the phalanges toward the little finger side of the hand, is a complex deformity occurring at the metacarpophalangeal joints (Fig 1). Its cause has been related to "bow-stringing" of the extensor tendons to the ulnar side (5), overpull of the abductor digiti quinti (5, 6), the gradual effect of gravity (3), and most recently to an imbalance of the flexor tendons secondary to synovitis (7). In addition to the ulnar subluxation, there is also volar displacement of the proximal phalanx (Fig 2). Reconstruction of this deformity requires relocation of the extensor tendons over the metacarpal head and reefing and interposition of the joint capsule. Muscles thought to perpetuate the deformity (abductor digiti V, dorsal interosseous IV) are released. Tendon transfers to stabilize the index finger for pinch (1st dorsal interosseous, extensor indicis proprius) are performed (Fig 3). Depending upon the condition of the articular cartilage, an arthroplasty of the metacarpophalangeal joint may be required, usually with temporary wire fixation (Fig 4A, B). In all cases, synovectomies of all of the metacarpophalangeal joints are performed. Postoperatively, a program of graduated exercises and



FIG. 2. The clamp is placed under the 1st dorsal interosseus which has displaced in a palmar direction along with the volar dislocation of the finger.



FIG. 3. First dorsal interosseus has been dissected free and is held by a retractor. Note extensor tendons which have displaced to ulnar side of each metacarpal head.

protective splinting is required to develop stable, painless joints with good motion and function.

SWANS-NECK DEFORMITY

Swans-neck deformity of hyperextension of the proximal interphalangeal joint with flexion of the distal joint is frequently encountered. It has at times been related to spasm of the volar interossei with subsequent dorsal displacement of the lateral bands (8). It would appear however, that it is a consequence of synovitis of the proximal interphalangeal joint. This could cause a loss of the

gliding mechanism of the flexor aspect of the finger with scarring of the synovial pouch of the volar plate, binding it down distally and leading to tendon imbalance (9). In addition, the extensor retinaculum can become bound down, causing a loss of its independent action (5) with resultant deformity (Fig 5).

The procedure most commonly used to correct this deformity is that described by Littler as the "intrinsic release" (10). In this operation the distal insertions of the intrinsic muscles are excised as indicated, since they are involved in the deformity either primarily or secondarily. If possible, the vertical fibers which



FIG. 4 A. Synovectomies and arthroplasties have been performed at all the metacarpophalangeal joints. Kirschner wires are drilled across for temporary fixation. B. The wires are cut short and the skin incision closed. Wires are easily removed three weeks later under local anesthesia.

flex the metacarpophalangeal joints are maintained with excision of only the oblique fibers which pass to the extrinsic extensor tendon. In more severe deformities the vertical fibers must be excised along with the actual bony insertions of the intrinsics. Several months of postoperative therapy are usually required before the complete benefits of the surgery are achieved.

BOUTONNIERE DEFORMITY

The boutonniere deformity of hyperextension of the distal joint with flexion of the proximal finger joint is believed to be secondary to rheumatoid granulations weakening the terminal portion of the central extensor slip as well as the transverse fibers which hold the lateral extensor slips in place. As a consequence, the lateral bands displace in a volar direction so that they cross anterior to the axis

of the joint becoming flexors of the proximal joint and overly strong extensors of the distal joint. The progress of this deformity is inexorable with the proximal joint protruding between the lateral bands as through a buttonhole, hence the name. Various techniques of surgical correction have been attempted with varying degrees of success. At times free tendon grafts have been employed, or the lateral bands sutured over the dorsum of the finger. At present, our choice for correction is simple tenotomy as described by Fowler (11). The distal insertion of the extensor tendon is severed, under local anesthesia, through a minute incision. The result is a "mallet-finger," or a dropped distal phalanx, equally uncosmetic but considerably more functional.



FIG. 5. "Swans-neck" deformity of middle finger (flexed distal joint, hyperextended proximal joint). "Boutonniere" deformity of ring finger (hyperextended distal joint, flexed proximal joint).

THE THUMB

The thumb has been referred to as representing 40 per cent of hand function (12). The functional disability may be far out of proportion to the degree of anatomic loss. Involvement of the thumb is unfortunately quite common in rheumatoid disease of the upper extremity.

The deformity seen most often is that adducted thumb with flexion contracture of the metacarpophalangeal joint and hyperextension of the interphalangeal joint (Fig 6). In addition, lateral instability may be present at one or both joints.

The normal arrangement of tendons on the dorsum of thumb is unusual. The extensor pollicis longus tendon passes over the metacarpophalangeal joint on its way to the base of the distal phalanx which it extends. The extensor pollicis brevis extends the proximal phalanx but also sends fibers to the dorsal hood which functionally binds it to the long tendon. The intrinsic muscles of the thenar eminence likewise send fibers to both edges of the hood so that all these muscles can act, directly or indirectly, as extensors of the distal thumb phalanx. With

synovitis at the metacarpophalangeal joint, the hood fibers stretch and the bony insertion of the short extensor is destroyed. The long extensor likewise is pulled to the ulnar side. This tendon imbalance, combined with continued use of the thumb for palmar pinch, leads to the deformity described. In addition, the carpo-metacarpal "saddle joint" of the thumb may become involved and require treatment as part of the adduction contracture. Frequently, as a consequence of both rheumatoid disease and abnormal use, lateral instability may develop in any or all of the three thumb joints. It is the lateral instability which demands stabilization (2).

If both the metacarpophalangeal and interphalangeal joints are unstable, fusion of both may be required. It is preferable that only one joint be fused. This will provide stability in prehension, while the motion remaining in the other



FIG. 6. Unstable grasp as distal thumb joint hyperextends.

joint will allow effective grasp of objects of various shapes. In our own experience, it is the interphalangeal joint which most commonly requires arthrodesis. Flatt (2) has devised a hinged metal prosthesis to replace arthritic finger joints. This has been adapted for the thumb with long prongs to provide motion at one joint and fusion at the next. The question of the ability of osteoporotic bone to support a metal prosthesis with moving parts has not yet been answered, and Flatt himself has stressed the experimental nature of this intriguing concept.

For severe adduction contracture, excision of the greater multangular along with appropriate soft tissue and skin releases (13) may be required as a preliminary step. Here too, postoperative exercises are required to insure the operative gains.

DISCUSSION

It would be inappropriate in a discussion of surgery of the rheumatoid hand not to stress the role of protective splinting, physical therapy and occupational therapy. Any procedure to mobilize joints will be successful only if the muscles

which move that joint can be strengthened to the point of controlled function. Likewise, until then the joint must be protected from undue stress by splinting. Dynamic splinting, using elastic and springs as assistive devices, combines both immobilization and rehabilitation through active motion.

The old concept of delaying surgery until the disease is quiescent has been discarded. Patients may be safely operated upon at any time, excluding of course, during an acute flare-up of the disease. The influence of prolonged steroid administration as an operative problem of adrenal suppression or as a surgical question of the effects of hypercortisonism on healing of bone, tendon and skin has not been great. Patients may be operated upon safely under regional anesthesia and tourniquet control, greatly minimizing systemic effect. Care must be taken to select properly motivated patients who can tolerate physically a program of postoperative rehabilitation, and psychiatrically the loss of their disability and the challenge of independence. The passive dependent personality seen in many rheumatoid arthritides must likewise be supported.

CONCLUSIONS

The treatment of any chronic progressive disease for which there is no cure calls for early prophylactic care. Since at this time there is no medication which can induce remission in rheumatoid arthritis nor halt the progress of the disease, treatment is limited to relief of symptoms with an assortment of drugs of varying degrees of toxicity (14). Surgical treatment, as an additional weapon in the relief of pain and disability would clearly be of value if applied early when a simple procedure might restore painless function, rather than later when major reconstruction is required to achieve the same end. Certainly the patient with a high titer latex fixation or with prominent joint involvement should be considered for possible prophylactic synovectomy. Early finger and thumb deformities should be restored to normal before advanced secondary changes occur. Spontaneous tendon ruptures should be diagnosed and corrected early.

It is our feeling that surgery can be a significant adjunct in care of the rheumatoid patient; it should not be delayed until the rheumatoid changes become irreversible and the patient's use of his hands impaired.

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Duodenal Ulcer In Aberrant Pancreas: Case Report and Review of Literature

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Aberrant pancreas was first described by Schultz in 1727 (1). The first histological studies were made by Klob in 1859 (2). Since that time, there have been numerous reports on aberrant pancreas:

Poppi (3)	(1935)	300 Cases
Barbosa (4)	(1946)	430 Cases
Krieg (5)	(1958)	200 Cases

In the early 20th century discussion of aberrant pancreas concentrated upon anatomical and pathological findings, but later, interest centered upon its complications and associated conditions. Many have considered aberrant pancreas either a rare and casual postmortem discovery or an unusual and interesting but incidental finding at operation.

PATHOLOGY

Aberrant pancreas always appears as a single, firm, round or irregular node, yellowish or white opaque lobulated with a granular surface. The histologic appearance is the same as that of the pancreas itself, with acini forming lobules which may or may not contain islet cells of Langerhans.

The reported incidence of aberrant pancreas varies from 0.55% to 5.6%. At the Mayo Clinic (5), one case is observed in every 500 cases of upper abdominal surgery.

The size of an aberrant pancreas ranges from 1.0 to 4.0 cm diameter. The most common location is the stomach, duodenum or jejunum; however, aberrant pancreatic tissue has been described in other abdominal sites, such as colonic diverticulum, mesentery, omentum, spleen, gallbladder, liver, etc. Some reported organ incidences in various series are as follows:

Author	Stomach	Duodenum	Jejunum	Ileum
Poppi (3)	31.46%	31.83%	21.7%	
Krieg (5)	31.5%	31.8%	21.8%	9.4%
Feldman (6)	27%	26%	20%	
Ritter (7)	35%	9%	40%	16%
Derbyshire (8)	24.2%	41.7%	25.2%	6%
Barbosa (4)	25.5%	27.7%	15.9%	2.8%

Within hollow gastrointestinal viscera, aberrant pancreatic tissue tends to be localized in the submucosa and may project into the bowel lumen. The histologic locations of ectopic pancreatic tissue as found by various pathologists includes:

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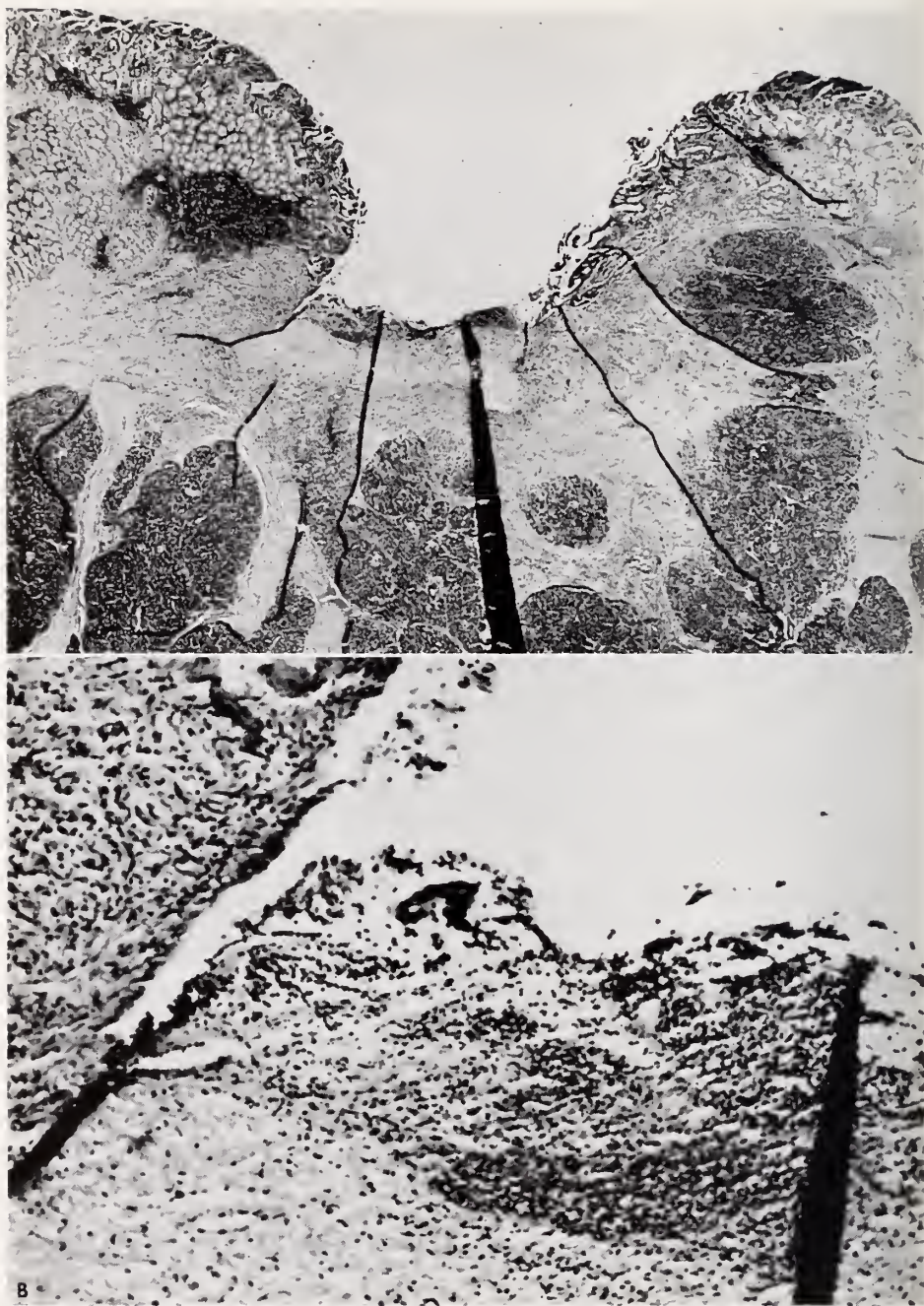


FIG. 1a. Aberrant pancreas and peptic ulcer.
FIG. 1b. Aberrant pancreas. High magnification.

Author	Intramuscular	Submucosal	Subserosal	Three Layers
Delhougne (9)	25.1%	45.5%	15.1%	4.2%
Barbosa (4)	23%	53.8%		
Marshall (10)	25%	60%		

Eighty percent of the aberrant pancreas in the duodenum usually occurs in the second portion of the duodenum. According to Feldman (6), the exact sites are:

Level of papilla.....	18
Proximal to papilla.....	35
Distal to papilla.....	5
Duodenal bulb.....	6
Pyloroduodenal junction....	1
Third portion.....	8

ETIOLOGY

Aberrant pancreas is attributed to faulty embryologic development of the pancreas, resulting in the misplacement of pancreatic tissue. Marshall (10) has subdivided the etiology into three categories:

1. Metamorphosis
2. Development
3. Chronic inflammation during fetal state.

SYMPTOMATOLOGY

Aberrant pancreas located in any part of the body may become enlarged as a result of inflammation or cyst formation, or by neoplasia, benign or malignant. If the aberrant pancreas is located in the duodenum, the symptoms present as similar to those in peptic ulcer with or without peptic ulcer formation by erosion of the tumor. Hemorrhage and perforation may focus attention on this otherwise unsuspected cell nest.

CASE REPORT

A 22 year old white man entered the hospital with a 24 hour history of tarry stool and some dizziness. He stated that he had been operated upon for perforated duodenal ulcer 18 months prior to admission, and had been treated with diet and antacid. He felt well for one year except for occasional abdominal pain, especially during the night. Physical examination revealed a patient in no acute distress with blood pressure 130/60 and pulse rate 110 beats per minute. The abdomen was soft, with slight tenderness in the epigastrium; no masses palpated. Rectal examination disclosed tarry stool. Laboratory studies on the day of admission disclosed the following values: Hemoglobin, 11.6 gm/100 cc; hematocrit, 36%; white blood cell count, 13,600; bilirubin, 0.4; blood urea nitrogen, 31; creatinine, 0.9 mg/100 cc; glucose, 80 mg/100 cc; amylase, 81 units/100 cc; cephalin flocculation, 1 plus.

The following day the hemoglobin level dropped to 9.5 gm/100 cc. An emergency gastrointestinal series revealed a marked deformity of the duodenal bulb with an active ulcer. A 12 hour overnight secretion study revealed 950 cc gastric fluid and 39.9 mEq/liter free acid.

At exploration, a round, firm mass measuring approximately 25 cm was palpated in the greater curvature site of the duodenum 2 cm from the pyloric ring. The mass was excised; pathologic examination revealed it to be aberrant pancreas. Corresponding to this nodule, there was a linear active ulceration measuring 1.5 cm by 0.9 cm, which had penetrated to the surface of the nodule. Acini were found in the aberrant pancreas (Fig 1a, b). A vagotomy and antrectomy with Billroth I anastomoses was performed. The postoperative course was uneventful.

DISCUSSION

Similar cases of aberrant pancreas in the duodenum complicated by ulcer formation were reported by various surgeons:

Author	Patient		Symptoms	Size of Tumor	Pathology	Treatment
	Age	Sex				
Marshall	26	♀	Epigastric pain, nausea, vomiting, 3 years	1.0 cm	Mucosal ulcer overlying tumor	Gastric resection
Barbosa	29	♂	Epigastric pain 2 years, one hemorrhage, 25 lb weight loss	3.0 x 1.5 cm	Ulcer overlying tumor, Acinar function (+)	Partial gastrectomy post-polya
	52	♂	Bleeding duodenal ulcer 2 years, Secondary anemia	Size unknown in 1st portion	Tumor in submucosa & submucosal, Acinar function (+)	Partial gastrectomy post-polya
	30	♀	RLQ pain 1 year	1.3 x 1.9 cm in 1st portion	Ulcer over tumor	Excision of ulcer and nodule, Mikulicz's pyloroplasty
Reiman	56	♂	Diabetes	Size unknown in 2nd portion	Acute ulcer, Acinar function (+)	
Branch & Cross	65	♀	Weakness, weight loss	Size 3 cm distal to pylorus	Acinar function (+)	Postmortem

Aberrant pancreas in the stomach with ulceration has also been seen. The peptic ulceration may be due to erosion by pancreatic enzymes which are secreted by the aberrant pancreas and digest the mucosa, or may result from the peptic digestion. Large nodules may produce incomplete obstruction and stenosis in the duodenum and thus contribute to the formation of ulcer. X-ray findings in cases of aberrant pancreas are generally not diagnostic. The nodule of the aberrant pancreas can be located in the upper gastrointestinal series of some cases, but nonspecific deformity and spasm of the duodenal cap are the more common findings. The acid secretion findings are not diagnostic. For aberrant pancreas in the duodenum complicated by peptic ulceration, partial gastrectomy including excision of aberrant pancreas is indicated.

SUMMARY

A case of peptic ulceration of an ectopic pancreatic nodule of the duodenum is presented and the pertinent literature is reviewed.

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Diffuse Small Intestinal Abnormality due to *Giardia Lamblia* with Roentgen and Clinical Reversibility after Therapy: Case Report

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It is known that *Giardia lamblia* infestation is asymptomatic in the host and produces no demonstrable change in the body of the carrier. It is also known that it produces distressing symptoms in the patient harboring it (1). It is not as widely appreciated that this normally innocuous protozoan may cause dramatic x-ray changes and accompanying clinical changes. The following case is presented to illustrate: 1. initial appearance of symptoms 2. diffuse x-ray changes in small intestine 3. disappearance of symptoms and regression of x-ray findings to normal on appropriate therapy.

CASE REPORT

H.K. a white female aged 43 years was in excellent general health until seen in mid April 1966 complaining of fatigue, malaise and frequent diarrhea of several weeks duration.

The patient had been in Morocco for a four day period in October 1965 where she felt well. In late December 1965 while at home in New York she developed nausea, diarrhea, temperature of 103 F lasting several days which was diagnosed as gastroenteritis of viral origin. She recovered within ten days and went to Mexico during the last ten days of January 1966 during which time she felt well.

In mid April 1966 patient insidiously developed poor appetite, fatigue, nausea, paraumbilical cramp like pain, watery diarrhea up to four movements daily. No blood was seen in the stools. The diarrhea seemed to be increased by the recumbent position but was less marked while sitting, standing, or walking. To exclude ulcerative colitis, amoebic dysentery or other large bowel diseases, sigmoidoscopy was performed and the finding of normal colonic mucosa for a distance of nine inches was reported. Several stool examinations revealed on one occasion an entamoeba and on another negative findings. Barium enema revealed no abnormal findings.

Symptoms of diarrhea, fatigue, malaise, paraumbilical cramps persisted, and April 29, 1966 a gastrointestinal series and small bowel examination were performed which showed the following findings. The stomach was normal. The duodenal bulb showed no deformity or ulcer crater, but the folds were markedly thickened and distorted. The duodenal sweep was normal in contour but there was marked uniform thickening of the mucosa. The folds appeared somewhat blunted in contour but uniform in size without evidence of ulceration or nodularity (Fig 1). Similar findings were noted in the jejunum with decreasing severity

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FIG. 1. Marked thickening and distortion of the folds of duodenal bulb, and duodenal sweep and jejunum. Folds are slightly blunted in contour, but the valvulae conniventes are symmetrical and uniform in appearance. There is some hypersecretion and considerable hypermotility. Thirty minutes after ingestion the barium has reached ascending colon.

distally. The jejunal loops were not dilated and exhibited no segmentation and only minimal hypersecretion without flocculation (Fig 1, 2). The valvulae conniventes were symmetrically and markedly thickened and were less pliable than normal. Again, no nodularity or masses were demonstrable along these altered



FIG. 2. Similar findings in jejunum, but ileum is normal in caliber with minimal thickening and distortion of the folds.

folds. The ileum showed similar but less severe alterations. Considerable hypermotility was noted, with the head of the barium column having reached the ascending colon in 30 minutes (Fig 1).

Because of these findings the patient was referred to a gastroenterologist (H.J.). Stool examination at this time revealed *Giardia lamblia* ova. Atabrine 0.6 grams daily for ten days was prescribed. The diarrhea stopped on the second day of Atabrine therapy. Following the ten day course of therapy, stools showed no



FIG. 3. After ten day course of Atabrine, duodenum, jejunum and ileum appear normal.

ova of *Giardia*, the patient felt completely well and has been well since. Repeat radiographic examination June 15, 1966 revealed an entirely normal small bowel examination (Fig 3).

DISCUSSION

The case presented above demonstrates diffuse and severe small bowel abnormality that can be produced by *Giardia lamblia*, and the complete reversibility of the process after Atabrine therapy. Marshak and Lindner (2) have recently

described a similar case with complete reversibility of small bowel findings after therapy. The roentgen findings described above must be differentiated from other small bowel enteropathies. In sprue, there is more bowel dilatation, segmentation and fragmentation. In Zollinger-Ellison syndrome, the small bowel findings are those related to hypersecretion, giving a reticulated pattern to the mucosal folds. In amyloidosis, there is less hypersecretion than in Giardiasis, and although the folds are also diffusely and symmetrically enlarged, they are sharper in outline and more uniformly affected throughout the small intestine. In Whipple's disease, the folds are less regularly thickened, and there is often a suggestion of nodularity along the mucosa. This may be associated with a moderate degree of dilatation, segmentation and fragmentation but less than in a typical case of sprue. In some cases of dysproteinemia, the edematous fold pattern in the jejunum can appear similar to that of Giardiasis. Diffuse small bowel lymphosarcoma may present primarily as a malabsorption pattern, but in these cases the thickened and altered valvulae lack symmetry and often present nodularity along the folds. Other parasitic infections such as hookworm and strongyloides may cause small bowel pattern similar to that seen in Giardiasis.

The points of clinical interest are the diagnostic response of the diarrhea and cramps to Atabrine (in less than 48 hours), the unquestionable relationship of the infestation to the patient's symptoms, and the moot point of its origin. Was the *Giardia* acquired in Morocco and was it quiescent for six months or was it incurred in Mexico with a two and half month latent period? Attention is called to the absence of other common intestinal parasites which frequently accompany *Giardia* and to the minimal evidence in the stools, as careful search revealed only occasional ova.

SUMMARY

A case of small bowel infestation with *Giardia lamblia* accompanied by severe diarrhea and abdominal pains is described. Diffuse small intestinal abnormalities were found on radiographic examination. Both the clinical and roentgenologic abnormalities reverted to normal after a ten day course of Atabrine.

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Effects of New 9,11-Dihalogenated Corticosteroids in Various Types of Alopecia. Part I

Clinical Studies in 32 Patients

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Following the report of anti-inflammatory activity in a series of C_{11} and C_9 -dihalogen-substituted corticosteroids (1), dichlorisone (9_α , 11_β -dichloro-1-pregnadiene- 17_α , 21-diol-3,20-dione-21-acetate) was found to possess particularly strong effect on skin structures (2). We have previously reported on the use of this drug in four patients with severe alopecia areata or universalis (3). The present report describes our clinical experiences with orally administered dichlorisone, 16-alpha-methyl dichlorisone alcohol (Sch 5882) and 16-alpha-methyl dichlorisone phosphate (Sch 10915) (Fig 1) in 32 cases of severe alopecia of varying origin.

MATERIALS AND METHODS

The types of alopecia and incidence by sex are shown in Table 1. The age range was 15 to 60. The duration of disease prior to therapy was 3 years to 34 years in alopecia universalis, 6 months to 30 years in severe alopecia areata, $2\frac{1}{2}$ to 18 months in postpartum alopecia, and 3 months to 10 years in traumatic-chemical (commercial hair straightener) patients.

Therapy was initiated with dichlorisone 400 milligrams per day, 16-alpha-methyl dichlorisone alcohol 40 mg/day or 16-alpha-methyl dichlorisone phosphate 30 mg/day in divided doses. At monthly intervals the dosage was adjusted according to the response in hair growth and side effects. When 16-alpha-methyl dichlorisone phosphate became readily available all subjects were changed to this medication. The minimum maintenance dose of the phosphate derivative in alopecia universalis and areata was 10 mg/day, and the maximum was 40 mg/day. Patients have been receiving therapy for two months to four years.

In postpartum alopecia and traumatic-chemical alopecia the medication could be progressively decreased after one month of therapy. Gradual lowering of the daily dose over a 3 to 6 month period was followed by 6 to 12 months of observation without medication.

The therapeutic stimulation of hair growth was evaluated by photographs of the scalp before and during therapy, observation of vellous hairs growing at the frontal hair line, and growth of terminal hairs on other parts of the body. Selected patients were monitored with standard tests of complete blood count, urinalysis, semen analysis, glucose tolerance, thyroid, renal, hepatic and adrenal function as well as ophthalmologic examination.

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**COMPARISON OF 9,11-DICHLORINATED CORTICOIDS
WITH HYDROCORTISONE**

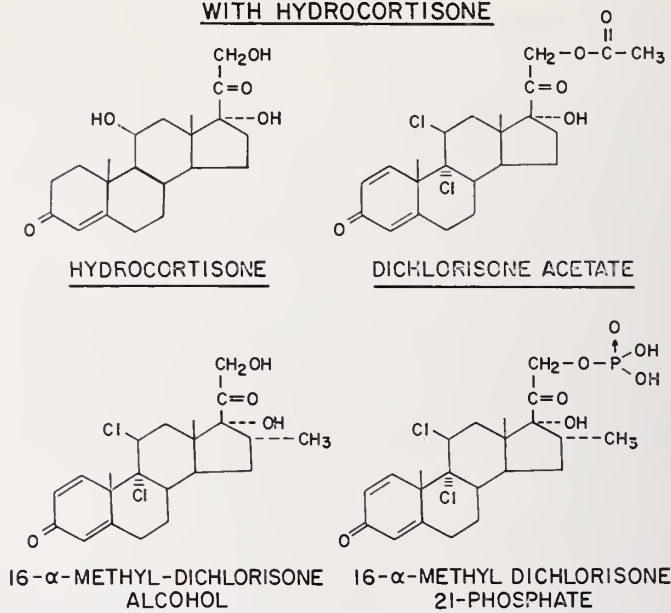


FIG. 1.

TABLE 1

Clinical Results of Oral Treatment of Alopecia with Dichlorisone, SCH 5882 and SCH 10915†*

Diagnosis	Total Cases	Male	Female	Therapeutic Results	
				Excellent or Good	Failure
<i>Type of Alopecia</i>					
Universalis	13	8‡	5	10	3‡
Severe Areata	11	6	5	11	—
Postpartum	5	—	5	5§	—
Traumatic-Chemical	3	1	2	3	—
ALL TYPES	32	15	17	29	3

* 16α-methyl-9α-11β-dichloro-1-pregnadiene-17α21-diol-3,20-dione-21-alcohol.

† 16α-methyl-9α-11β-dichloro-1-pregnadiene-17α21-diol-3,20-dione-21-disodium phosphate.

‡ Including one patient with congenital alopecia universalis.

§ Two episodes treated in one patient.

RESULTS

The results of treatment are summarized in Table 1. In alopecia universalis and areata regrowth of scalp hair was usually noted within four to six weeks of therapy and progressed with continuous administration of medication. Response

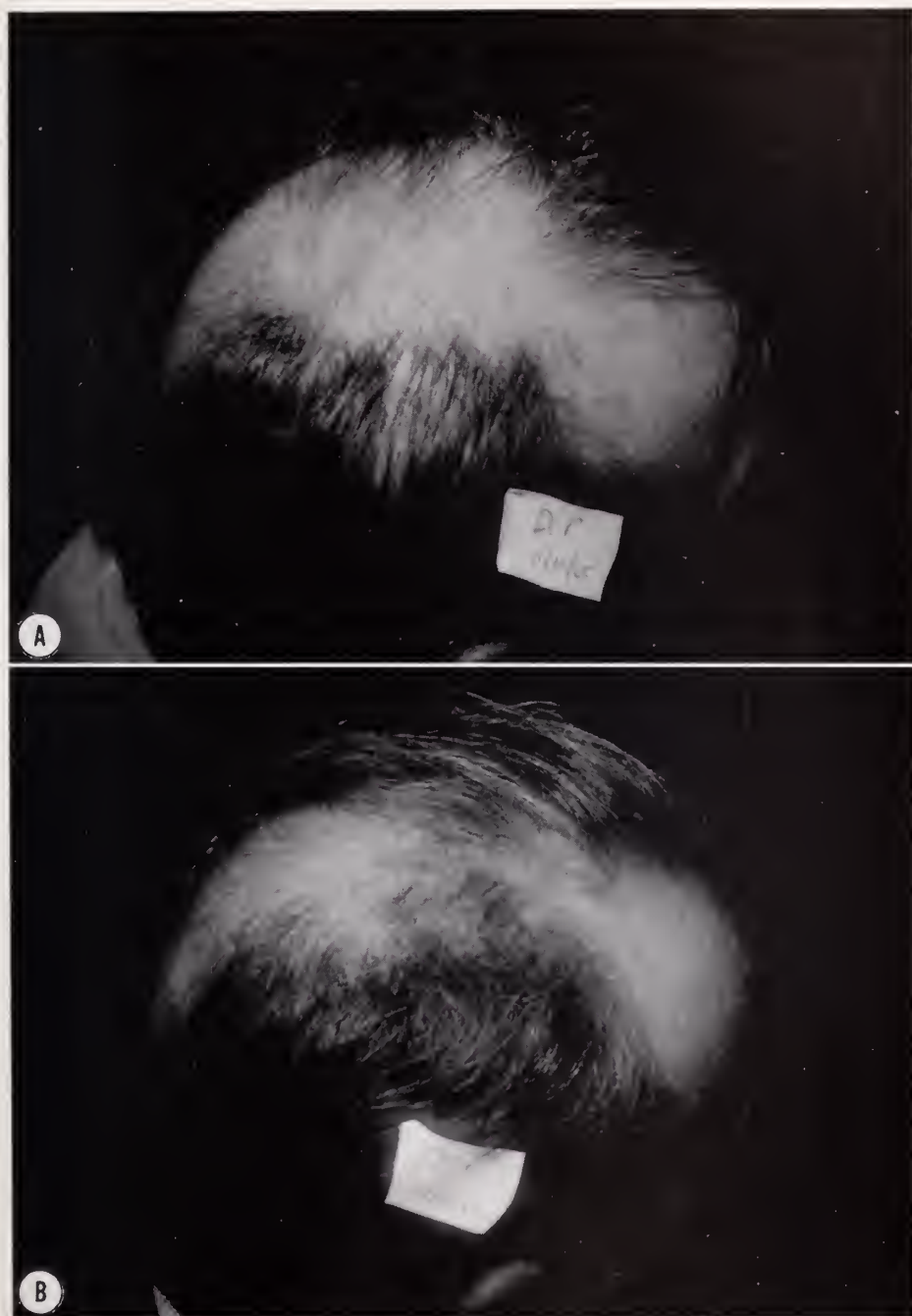


FIG. 2A. Patient D.P. Severe Alopecia Areata of 3 years duration, previously unresponsive to prednisone.

FIG. 2B. Patient D.P. after 4 months of therapy.

was more rapid and easier to obtain in patients with a shorter duration of disease. Among the alopecia universalis patients there were three failures. One subject 34 years old, had congenital alopecia universalis with tylosis and pachyonychia, a rare genetic ectodermal disorder. Another patient, with alopecia universalis for 31 years, regrew adequate hair on beard, eyebrows and body but failed to regrow scalp hair. A prior trial of prednisone similarly had been unsuccessful. The third failure, a 15 year old boy, regrew scalp and body hair but was unusually susceptible to side effects of Cushing's habitus which required cessation of therapy. Alopecia areata subjects responded well but not all of the areata patches regrew hair equally in patients with disease of long standing. Two patients with severe areata became refractory to smaller maintenance doses and required



FIG. 3A. Patient B.R. Severe Alopecia Areata of 9 years duration, previously unresponsive to prednisone.

FIG. 3B. Patient B.R. after 24 months of therapy.

increased amounts for adequate control. Four alopecia areata patients could be withdrawn from medication without recurrence of hair loss. Continuous maintenance therapy was required by the other subjects. The degree of hair regrowth in these diseases is demonstrated in figures 2A through 5B.

Patients with postpartum and traumatic-chemical alopecia (Fig 6A, B) demonstrated a gratifying cessation of excessive hair loss within four weeks of therapy. Return of normal hair growth continued as the dosage was gradually decreased and medication stopped within three to six months. Follow-up examinations revealed retention of the hair.

SIDE EFFECTS

Side effects of these dosages of dichlorisone compounds were generally similar to those of other glucocorticoid drugs (Table 2). However, in our experience the increased appetite, tendency to weight gain and sense of well-being were more

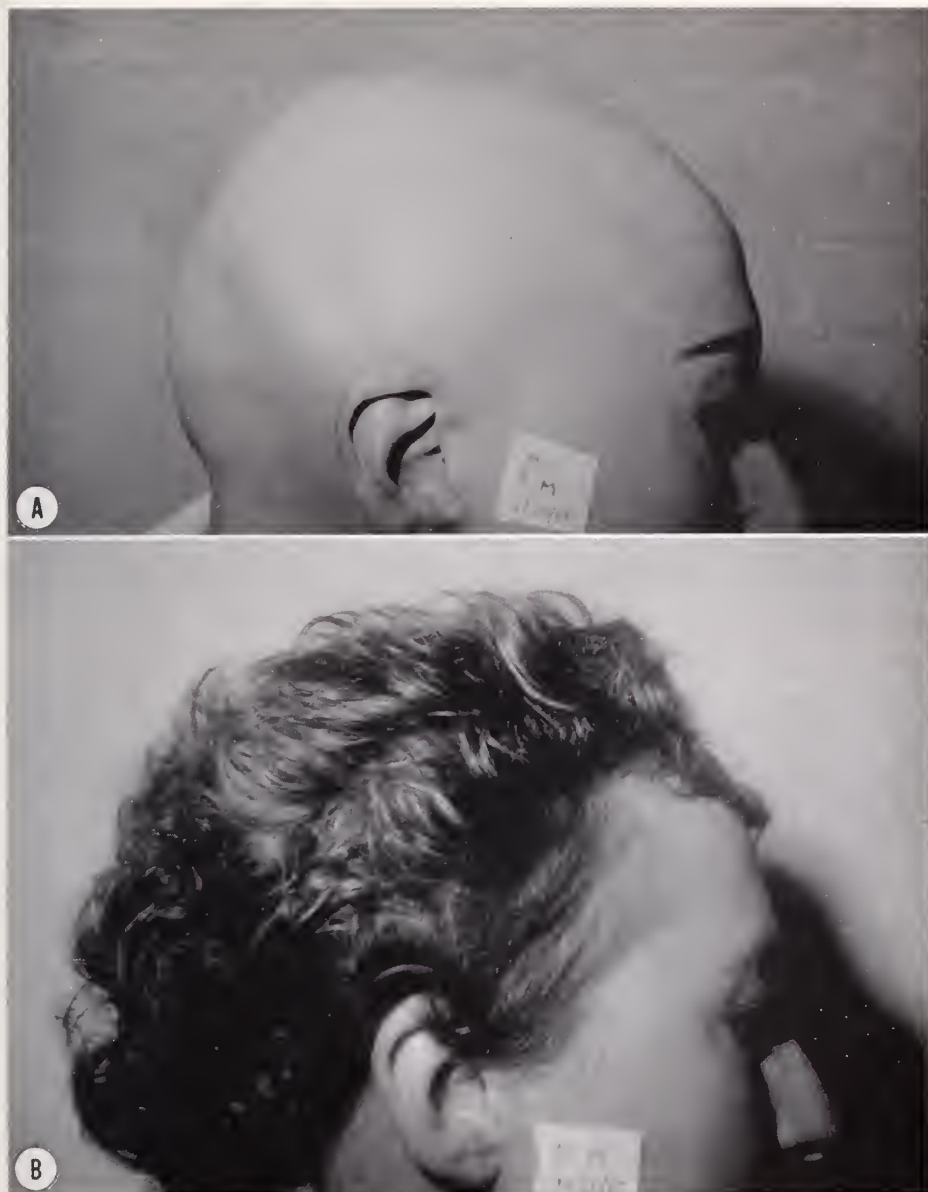


FIG. 4A. Patient R.M. Alopecia Universalis of 2 years duration.

FIG. 4B. Patient R.M. after 10½ months of therapy.

striking with dichlorisone and its derivatives. In addition, there was no hypertension or diabetogenic tendency. Prolonged duration of therapy was associated with a greater tendency to moon facies, despite a cessation of weight gain and the decrease to a maintenance dosage.



FIG. 5A. Patient C.N. Alopecia Universalis of 5 years duration.

FIG. 5B. Patient C.N. after 12 months of therapy.

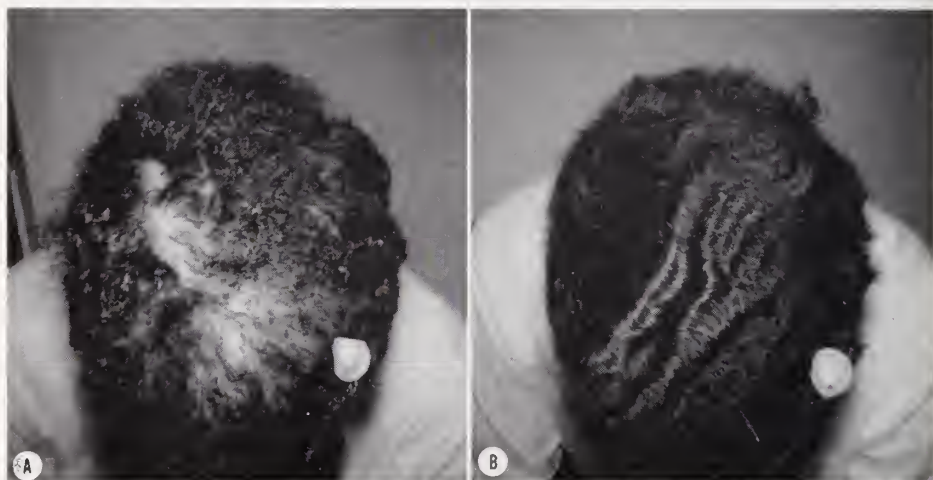


FIG. 6A. Patient S.G. Traumatic-Chemical Alopecia. Rapid progressive hair loss for 4 months.

FIG. 6B. Patient S.G. after 3 months of therapy.

Six cases of incipient posterior subcapsular cataracts developed among ten universalis or areata patients taking 30 to 40 milligrams per day of 16-alpha-methyl dichlorisone phosphate for over 18 months. This was noted at routine ophthalmologic slit-lamp examination and had not produced pronounced impairment of vision. In four cases the cataracts were bilateral; in two cases only one eye was involved.

The effects on pituitary and adrenal function are described in detail elsewhere (4). Significant decrease of the urinary total neutral 17-ketosteroids and 17-hydroxysteroids were demonstrated. Metapyrapone and Gel-ACTH tests suggested that suppression of the pituitary release of corticotropin was the most likely cause of the decrease in pituitary-adrenal responsiveness.

Three long term subjects who suddenly stopped therapy complained of steroid withdrawal symptoms (weakness, joint aches, skin rash) which required ACTH injections for relief. Gradual tapering of the dosage over a period of two to

TABLE 2

Side Effects in 32 Patients Treated with Dichlorisone, 16-alpha-methyl dichlorisone alcohol and 16-alpha-methyl dichlorisone phosphate for 2 months—4 years

Side Effect	Number of Patients
Increased appetite	30
Increased energy and well-being	15
Moon facies and plethora	13
Abdominal bloating	11
Excessive weight gain (over 10 lb)	8
Posterior subcapsular cataracts*	6
Hirsutism*	5
Upper gastrointestinal distress	5
Fluid retention	4
Transient skin rash	3
Mild insomnia	3
Striae	3
Cold sensitivity of teeth	3
Constipation	3
Cervical hump	2
Menstrual irregularity†	2
Nocturia	2
Acne	1
Muscle cramps and purpura	1
Hypertension, diabetic tendency	0

* 10 patients on long term (over 18 months) therapy.

† 17 females.

three months was not associated with any distress in 12 other patients whose treatment was discontinued.

No significant abnormalities were noted in complete hemogram, urinalysis, semen analysis, glucose tolerance, thyroid, renal or hepatic studies in selected patients.

DISCUSSION

Oral glucocorticoid treatment with 150 milligrams per day cortisone acetate or its equivalent can arrest hair loss and restore active hair growth in most patients with alopecia areata and universalis within four to six weeks (5, 6). Generally the therapeutic response depends on the duration of alopecia, the

long-standing condition being less amenable to treatment (6). However, maintenance doses are usually so high as to produce cushingoid appearance in all patients (7—11), and dangerous glucocorticoid side effects of hypertension and hyperglycemia in some (12—14). The doses of dihalogenated compounds used in this study exerted a similar potent influence upon the hair follicle. The usual medical precautions and contraindications should be observed with dichlorisone compound usage as with other glucocorticoid therapy.

Posterior subcapsular cataracts as a complication of long term corticosteroid therapy have been reported frequently in patients with rheumatoid arthritis and with less frequency in other disease such as nephrosis, asthma, lupus and sarcoidosis (15, 16). Our study describes the development of incipient posterior subcapsular cataracts in 6 of 10 alopecia patients treated with 30 milligrams per day 16-alpha-methyl dichlorisone phosphate for at least eighteen months. This observation has not been reported previously in alopecia patients treated with steroids.

Postpartum alopecia (17), and traumatic-chemical alopecia with rapid hair loss was severe in our patients and accompanied by marked psychic trauma. All responded well on low dosage, relatively short term therapy. Therefore side effects were minimal and no incipient subcapsular cataracts occurred in these subjects.

SUMMARY

The oral administration of new closely related 9,11-dihalogenated corticosteroid derivatives, Dichlorisone (9 alpha, 11 beta dichloro 1,4-pregnadiene-17 alpha, 21 diol-3,20 dione-21-acetate, 16 alpha methyl-dichlorisone-21-alcohol (Sch 5882) and 16-alpha-methyl dichlorisone disodium-phosphate (Sch 10915) have been found to possess potent stimulatory effects on the human hair follicle. In clinical study of 32 cases of alopecia universalis, severe alopecia areata, postpartum or traumatic alopecia, each drug was found capable of arresting excessive hair loss and restoring active hair growth within four to six weeks of therapy at doses ranging between 20 and 40 milligrams daily. Adverse effects included the development of incipient posterior subcapsular cataracts in 6 of 10 patients treated for over eighteen months, a steroid complication not previously reported in glucocorticoid treatment of alopecia. Side effects similar to other glucocorticoid compounds were also noted, except for the absence of hypertension and diabetogenic tendency with the doses used in this study.

Dichlorisone, Sch 5882 and Sch 10915 used in this study was supplied by Dr. Jack Black and Dr. Frank Falco of Schering Corporation, Bloomfield, New Jersey.

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Effects of New 9,11-Dihalogenated Corticosteroids in Various Types of Alopecia. Part II.

Pituitary-Adrenal Responsiveness in Patients Treated with 16 α -Methyl-Dichlorisone Alcohol

SOLOMON I. GRIBOFF, M.D. AND WALTER FUTTERWEIT, M.D.

Interest in compounds of the dichlorisone (9 α , 11 β -dichloro-17 α , 21-dihydroxy-pregna-1, 4-diene-3, 20-dione) series has been stimulated by the search for potent anti-inflammatory steroids that are free of the undesirable pharmacologic effects associated with the glucogenic steroids. The dichlorisone compounds are unique structurally in that there is a chlorine atom substituted at the 9- and 11-carbon positions. The first analogue which showed promise was dichlorisone-21-acetate. This compound has been used for the treatment of patients with various types of alopecia (1, 2). The present study was performed to evaluate the suppression of pituitary-adrenocortical function accompanying the therapeutic administration of the closely related 16 α -methyl-dichlorisone alcohol (Fig 1).

MATERIALS AND METHODS

The patients were 30 men and 5 women all without organic disease except for the presence of some degree of baldness. They received 30 to 40 mg 16 α -methyl-dichlorisone alcohol orally in divided doses daily. The age range was between 14 and 54 years. The total neutral 17-ketosteroid determinations were performed on 24 hour urine specimens using a modification of the Drechter method (3). The urinary 17-hydroxycorticoids were analyzed using a modification of a standard method (4). Twenty-five of the patients were studied by comparing the control urinary steroid value with the corresponding value while on therapy.

The metyrapone (Su-4885) test was performed in all 35 patients during therapy by the administration of 750 mg metyrapone orally every four hours for six consecutive doses beginning at 8 AM (5). Analysis of urinary 17-hydroxycorticoids was performed in a control 24-hour specimen and a 24-hour collection the day following administration of Su-4885. Plasma 17-hydroxycorticoids were determined by using a modification (6) of the method of Silber and Porter.

A two hour intramuscular Gel-ACTH test (7) was performed on 18 of the patients. A response was considered adequate when there was a two-fold increase in the free plasma 17-hydroxycorticoids two hours after the intramuscular administration of 40 units purified Gel-ACTH. In six patients who were receiving continuous therapy for six months, the Soffer and Gabrilove (8) water load test was performed two days after discontinuing the administration of 16 α -methyl-dichlorisone alcohol.

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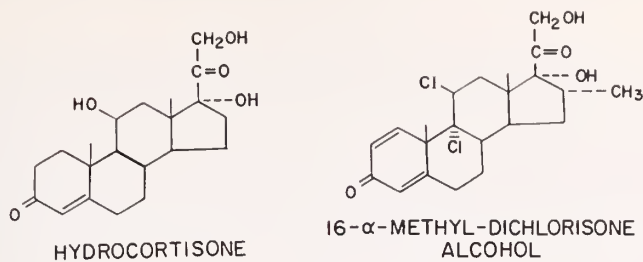


FIG. 1.

TABLE 1

Urinary total natural 17-ketosteroid determinations (mg/24 hr) before and after oral therapy with 16α-methyl-dichlorisone alcohol (30-40 mg/day)*

Patient	Sex	Before	After
Therapy 3-4 Months			
1. H.S.	M	12.1	8.0
2. J.V.	M	10.4	2.3
3. M. Sch.	M	14.7	6.3
4. R.A.	M	14.9	2.1
5. H.B.	M	5.8	3.1
6. M.G.	M	9.3	3.2
7. W.W.	F	7.3	5.5
8. M. Se.	F	9.5	2.2
Therapy 5-11 Months			
9. D. Va.	M	7.2	4.0
10. L.D.	M	12.0	3.1
11. D.S.	M	8.0	1.2
12. R.G.	M	16.9	4.7
13. S.O.	M	17.6	10.5
14. N.P.	M	13.3	7.3
15. J.B.	M	18.5	5.8
16. E. Se.	M	17.7	6.5
17. R. De.	M	7.2	3.3
18. E.N.	M	6.7	3.3
19. D. Vi.	M	11.3	5.1
20. E. Sh.	F	5.4	4.4
21. A.B.	F	10.5	2.1
Therapy 12-30 Months			
22. R.E.	M	4.8	4.8
23. R.B.	M	10.0	3.1
24. W.G.	M	8.0	4.5
25. R. Da.	M	16.5	4.7

* Normal range at Mount Sinai Hospital: Adult Females—5-13 mg/24 hr; Adult Males—7-18 mg/24 hr

TABLE 2

Urinary 17-hydroxysteroid determinations (mg/24 hr) before and after oral therapy with 16 α -methyl-dichlorisone alcohol (30-40 mg/day)*

Patient	Age	Before	After
Therapy 3-4 Months			
1. H.S.	20	11.0	2.9
2. J.V.	34	8.9	1.6
3. M. Sch.	27	8.3	3.4
4. R.A.	25	10.2	3.9
5. H.B.	35	11.8	4.3
6. M.C.	19	12.0	3.9
7. W.W.	31	5.5	4.5
8. M. Se.	38	10.4	2.7
Therapy 5-11 Months			
9. D. Va.	28	3.0	1.5
10. L.D.	44	10.0	5.7
11. D.S.	32	9.5	3.4
12. R.G.	31	14.3	10.4
13. S.O.	28	7.5	3.5
14. N.P.	29	8.6	2.8
15. J.B.	23	9.6	1.8
16. E. Se.	20	14.0	5.3
17. R. De.	27	4.5	3.1
18. E.N.	50	6.9	3.2
19. D. Vi.	37	7.8	2.7
20. E. Sh.	45	6.6	0.3
21. A.B.	32	4.9	4.1
Therapy 12-30 Months			
22. R.E.	14	3.8	0.5
23. R.B.	20	9.4	1.9
24. W.G.	54	4.2	2.4
25. R. Da.	27	6.4	3.1

* Normal range at Mount Sinai Hospital: 3-14 mg/24 hr

RESULTS

The effect of long-term daily oral administration of 30 to 40 mg 16 α -methyl-dichlorisone alcohol on urinary excretion of the total neutral 17-ketosteroids and 17-hydroxycorticoids is shown in Tables 1 and 2. A significant decrease from control urinary values was almost uniformly found in all patients for both the urinary total neutral 17-ketosteroids and 17-hydroxycorticoids. This decrease was evident after three to four months of continuous therapy.

Table 3 demonstrates adequate responsiveness to metyrapone in 19 of 35 patients treated for prolonged periods. Of seven patients who were withdrawn from

therapy, six demonstrated an adequate metyrapone response when tested from three weeks to three months after withdrawal of the medication. Previously all seven patients showed impaired responsiveness to metyrapone while on continuous therapy for a period of 3 to 12 months.

The response of free plasma cortisol to the exogenous administration of Gel-ACTH was adequate in 16 of 18 subjects tested (Table 4). Fourteen of these patients demonstrated an inadequate metyrapone test. All six patients who received the water load test responded normally.

TABLE 3
Metyrapone Test During Therapy*

Months Therapy	Number Patients	Adequate Response	Inadequate Response
3-4	13	8	5
5-11	12	5	7
12-30	10	6	4
Total	35	19	16

* 750 mg Metyrapone every 4 hours for 6 doses

TABLE 4
Intramuscular Gel-ACTH Free Plasma Cortisol Test During Therapy*

Months Therapy	Number Patients	Adequate Response	Inadequate Response
3-4	7	6	1
5-11	7	6	1
12-30	4	4	0
Total	18	16	2

* Two-fold increase in free plasma 17-hydroxycorticoids 2 hours after 40 units of Gel-ACTH intramuscular

DISCUSSION

The prolonged daily oral administration of 30 to 40 mg 16 α -methyl-dichlorisone alcohol is associated with some degree of suppression of pituitary-adrenocortical responsiveness. This is demonstrated by a significant decrease in the urinary excretion of the total neutral 17-ketosteroids and 17-hydroxycorticoids. The effect is probably due to the suppression of pituitary release of corticotropin (1, 7) as evidenced by the failure in 16 of 35 patients to respond to metyrapone while only 2 of 18 subjects failed to respond normally to Gel-ACTH. Whether 16 α s methyl-dichlorisone alcohol, in the amounts employed in this study, has less pituitary-adrenal suppressive effect than other glucogenic steroids cannot be answered by our data.

SUMMARY

Pituitary-adrenal responsiveness was studied in non-endocrine patients while on prolonged daily oral administration of a new synthetic steroid, 16 α -methyl-dichlorisone alcohol. Significant decreases of the urinary total neutral 17-ketosteroids and 17-hydroxycorticoids were demonstrated. An inadequate response of the urinary 17-hydroxycorticoids to metyrapone was noted in 16 of 35 patients on continuous therapy. Only 2 of 18 patients failed to respond adequately to the exogenous administration of Gel-AC²TH. Suppression of pituitary release of corticotropin is the most likely cause of the decrease in pituitary-adrenal responsiveness in patients on long term therapy.

The 16 α -methyl-dichlorisone alcohol was supplied by Dr. Jack Black, Schering Corporation, Bloomfield, New Jersey.

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Psychiatric Aftercare: An Opportunity And A Challenge

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Robert H. Felix, in accepting the 1964 Samuel Rubin Award at the Post-Graduate Center for Mental Health in New York City, said about Psychiatry in this country in 1975: "The dichotomous concept of out-patient versus in-patient care will disappear to a large extent because—as is true with other illnesses—hospitalization will be viewed more as an extension of the care and treatment a physician otherwise provides—used because it provides the appropriate facilities to meet the needs of the patient at that particular stage of his illness." (2)

There was a time when a person's history of illness began with his hospitalization. Due to a lack of health education, a person's concern with his health began when an illness became acute and required hospital care. Concern with physical health has now shifted to the longitudinal outlook. The individual is examined periodically from infancy on, traces of illness are detected early and a number of disease entities are eliminated by effective preventive measures. Hospitalization, then, becomes a phase, usually short, in the personal protocol of health and illness, with care and treatment reverting to the usual ambulatory care continuum as soon as possible.

In the area of mental health, illness still too often begins with the acute phase that requires immediate hospitalization. This seems particularly true in lower socioeconomic groups because of a lack of awareness concerning mental health, and in higher socioeconomic groups because of a denial of evidence of mental illness due to an exaggerated concern with maintenance of social status and prestige. In the area of mental health we are still struggling with the artificial separation between mental health and mental illness; between in-patient care and out-patient care; between what constitutes the somatic and the psychic. The longitudinal, unified and integrated attitude toward mental illness and health is one factor in the long-term goal toward erasing the distinctions between psychiatry and other medical disciplines. In this frame of reference the first psychiatric hospitalization becomes a challenge and opportunity for unifying the dichotomies mentioned above and for providing services to individual and community that will eventually demonstrate holism in medicine to be a live concept.

Why out-patient rather than in-patient care? After all, is not aftercare an

Continuation of a paper on psychiatric aftercare published in this Journal in 1965 (1).

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Presented at the Monthly Departmental Conference, March 9, 1966 by the staff of the Aftercare Clinics of the Institute of Psychiatry: Samuel L. Safirstein, M.D., Chief, Peter Laquer, M.D., Maurice Osinoff, M.D., Bertrand Jacobs, M.D., Edmund Slakter, M.D., Warren Seides, M.D., Sheldon Capp, M.D., Frank Sorensen, M.D., and Irving Friedman, M.D.

extension of and therefore dependent upon the prior existence of hospitalization and in-care? If in-patient care begot aftercare, is it not presumptuous for the child to attempt more than the parent? In part, a reversal of traditional roles is being introduced. As Felix indicated in his address, it is the trend in medicine to substitute out-patient medicine for in-patient medicine, or to put it differently, ultimately to replace treatment with prevention. Hospitalization as an episode in the person's history of health and disease becomes shorter in duration as time goes on. This is possible because of advanced medical technology and attempts to reduce the increasing cost of hospital care. However, what really matters in the philosophy of shorter hospital care is the prevention of regressive tendencies and their ankylosing effects on the individual's psychic functioning. It is no longer a matter of expedience or money to keep hospital stay at a minimum, but it is good medicine to see that the individual be returned to family and community as soon as possible.

As a matter of fact, whenever longer hospitalization becomes a necessity, conditions are created within the institution that resemble life on the outside. The concept of therapeutic community and patient self government are expressions of this attitude (3). Reparation, restitution and reintegration of function become the primary goal of in-patient care; consolidation of these has been the traditional aim of aftercare. We are now attempting to extend its function to prevention. Through aftercare we are trying to reach out to the family and the community. Hospitals have traditionally emphasized in-patient care; this has been their business. They still do so to a great extent. The emphasis is slowly shifting toward out-patient care and the trend toward increasing the out-patient departments and decreasing the number of beds. There is definite deemphasis of the "bed-centered" approach. As the physician works toward the ultimate elimination of the need for his services, so do hospitals work toward ultimate elimination of the need for in-patient services. Ultimate goals are never reached; what we want to emphasize here is that the scope and outlook of out-patient services including aftercare can be much wider and more encompassing than that of in-patient care.

The question comes to mind at this point: If the out-patient approach is so important, why has it been so badly neglected in the history of hospital medicine? Terms like "Siberia," "stepchild" or "bargain basement" of hospital medicine have been aptly applied to the OPD departments of hospitals (4). One reason for this neglect is the general human tendency to concentrate on parts for the purpose of mastery, especially so, when the whole is elusive. To treat a symptom when its origin is unknown is natural, but to insist on the symptom when the disease behind it is known and understood is poor medicine. The "ad hoc" approach to medicine becomes untenable when the total spectrum of patient care becomes discernible. In-patient services have held the attention of the medical and nonmedical world because that was the place where the drama of medicine was being played; there was the excitement. The OPD was a dull and dreary place which the physician had to endure before getting to the in-services where things became exciting. Thus developed a new dichotomy of first and

second rate hospital services, first and second class patients and first and second class physicians. This is beginning to change. It is appropriate to introduce here in abbreviated form the five principles essential to high quality medical care as stated by George James in 1964, when he was New York City Health Commissioner: 1. Comprehensive care programming in which the patient would be treated not only for his chief complaint but also for all problems related to it. 2. Continuity of care, in which the same physician would attend the patient throughout all illnesses. 3. Family-centered care. 4. Professional competency, with the members of the attending staff assigned to the out-patient department, and assignment there to be considered as important to the staff as in-patient care. 5. Community orientation in regard to home care, narcotic addiction, and chronic illness (4).

So far, I have been considering aftercare as a part of the out-patient department, which it is. However, there are features which distinguish it from other out-patient clinics and services. There is a special aftercare feeling and spirit that comes from having been an in-patient and actually slept and lived in the hospital. This brings a strong sense of belonging, of participation and almost proprietary ownership. It is not just a peripheral periodic visit to the clinic for a session, with a glimpse at an occasional fellow patient in the waiting room that ties the patient to the hospital and staff—although we know how powerful such ties can be. It is having lived with fellow patients in a circumscribed space day and night, sometimes for three months or even longer, having practically lived with members of the staff, shared in a small but eventful community life, having perhaps witnessed an attempted suicide—all this contributes to the most powerful human attachments. Patients who notoriously have a difficult time forming lasting and meaningful relationships form strong friendships while on the ward, and for a long time return to visit after being discharged. Occasionally we have direct and concrete evidence of how the attachment that comes from being an in-patient transcends transference relationships prior to hospitalization. When patients of the OPD psychiatric clinics require hospitalization they invariably request to be followed in aftercare by their ward therapist, a resident in training, rather than to return to their previous therapist in the OPD clinic, although this is usually a more experienced psychiatrist. It also happens occasionally that a patient who is referred by a private psychiatrist makes the same request, despite at times a long and trusting relationship with the private psychiatrist.

In commenting upon the powerful attachment that an in-patient develops towards the ward, the Department of Psychiatry and the hospital—something we call "Mount Sinai transference" (5)—I cannot help pointing out the differences when we compare this situation with obstetrical cases of women who come to the hospital to deliver. For them the hospital and its services are ancillary while their individual doctor and the relationship with him are of paramount importance. Psychiatric patients are and/or feel weak and vulnerable. They need and gravitate toward strength. The Mount Sinai complex seems to them much stronger than any particular individual.

There are other implications that flow from the patient's attachment to the ward and the hospital which are relevant to aftercare. The weak patient not only follows strength, direction and structure; most of our very sick patients avoid closeness, mutuality and involvement. Closeness spells being swallowed up to them, mutuality spells responsibility, involvement spells participation. All three require functioning on the emotional level for which most of our patients are too alienated. A close, one-to-one relationship with an individual therapist is often very threatening to the patient and brings with it a tendency to "act out" inside or outside the therapeutic relationship, or brings a premature wave of negative transference which cannot be handled. This may take place when the therapist is not experienced and tries to get close to the patient too soon. Certain of our patients have great difficulty in accepting their positive feelings toward their therapist. In contrast to individual transference, institutional transference is much more comfortable to the patient. It is impersonal and relates to a ward, a building, a hospital or a clinic. Not one person but many people are involved in the concept of institutional transference. Feelings can remain on the surface as with attachments to personnel. They are of a passing nature and require no commitment. The hospital has no claims on the patient and expects nothing in return. It is there, big, tall, strong and immutable whenever the patient needs it. We are dealing here with a diluted and displaced form of transference (5).

What actually takes place is a dual relationship that the patient develops, one to the individual therapist and another to the institution or to the hospital, with both present to varying degrees depending upon the extent of the patient's sickness. It seems that the sicker the patient the more heavily he will lean toward institutional transference than toward individual transference and vice versa. It becomes very important to diagnose which type of transference is to be emphasized in the treatment of a given patient. Some of our patients may not be able to enter into a meaningful individual relationship, but they all have an important relatedness to the ward and to the hospital. These patients can accept a supporting individual relationship as long as it is distant, infrequent, and does not expect anything personal from them in return.

The most diluted relationship that the Aftercare Clinic offers to certain of its patients is its Medication Clinic, which is attended by some fifty patients. They come once in two weeks for renewal of their prescriptions. Some have a brief interchange with the therapist, some have requests for social or situational help as well. The therapist is alert to these possibilities and ready to deal with them on the level of the patient's capability.

An interesting phenomenon has recently been reported by the psychiatrist in charge of the Medication Clinic. A number of the chronic patients who had been declared no longer able to benefit from psychotherapy, when relieved of the expectant and at times insistent attitude of their previous psychotherapists, began to move towards their new therapist, spend more time with him and talk more freely about personal matters. The attitude toward the Medication Clinic as a "wastebasket" for psychotherapeutic failures has to be drastically revised.

These patients need a different approach, different timing and a different handling. Some of them may find their way back to psychotherapy, despite the fact that they continue to require drugs.

I have tried to emphasize the impact a hospitalization has on a psychiatric patient and how the fact that he has been an in-patient makes him different from other psychiatric OPD patients. Although aftercare is part of OPD and the aftercare patient *is* an out-patient, I see him as closely related to the in-patient services as to the out-patient services. I see the in-patient and the aftercare patient as one. This is the uniqueness of the aftercare patient. He straddles the threshold of the hospital with one foot in it and one foot out of it. The other out-patients' relationship to the hospital is but tangential. Aftercare is the bridge between in-patient and out-patient care. I look to aftercare to eventually eradicate the in- and out-patient dichotomy. However, before it can do so, it has first to fulfill certain criteria. Since it straddles the threshold between hospital and community, aftercare has to become community oriented and community minded. The road to the community is the family.

Before I continue, I would like to present a brief summary of our mode of operation. For many years the census in the Aftercare Clinic was about 50 patients. After the opening of the Institute of Psychiatry at the end of 1962, the census reached 272 on January 1, 1965 (figures quoted here are exclusive of the Day and Night Center, which has its own aftercare services).

The basic therapeutic unit is the resident-patient relationship which was begun on the ward and continues in the Aftercare Clinic. About 25 first and second year residents form the therapeutic staff. Eight members of the attending staff act as supervisors, teachers and administrators. Training runs parallel to rendering of services. The therapeutic model of goal-directed psychotherapy begins while the patient is on the ward and continues in the Aftercare Clinic. Drugs and other ancillary services are also used. Social Service is actively engaged in casework therapy with significant relatives, but is patient centered. Basically, it can be said that we use the caseworker to help the relative to become more tolerant and more accepting of the patient and his needs. Since it is difficult to gain the relative's selfless cooperation in terms of the patient, some casework has to be done with the relative himself, but the emphasis remains on the patient. The caseworker begins her relationship with the relative while the patient is on the ward. This continues after the patient moves to the Aftercare Clinic. Thus we have two uninterrupted relationships on parallel levels; between resident and patient and between relatives and caseworker. Doctor and caseworker are in frequent consultation and conferences including the supervisors of both are held when indicated. The parallel axis of doctor-patient and caseworker-relative are the mainstay of therapy and training, and have successfully passed the test of the basic working model in the Department of Psychiatry.

The use of psychological services completes the basic team of doctor-case-worker-psychologist. Psychodiagnostic evaluations of the patient on the ward and/or later during the patient's stay in Aftercare Clinic are performed at the doctor's request.

Often the patient is discharged by his original therapist. When this takes place, contact between caseworker and relative stops as well. Not infrequently, however, because of the nature of the patient's illness, the psychotherapeutic goals posited, and at times because admission to the Aftercare Clinic occurs close to the time the original therapist leaves the service, it becomes necessary to transfer the patient to a different therapist for continued aftercare. In this case contact between caseworker and relative continues unchanged.

In addition to psychotherapy, other therapeutic means are used for the benefit of the patient. These are: group therapy, occupational therapy, recreational therapy, electroshock therapy and the previously mentioned Medication Clinic. In other words, aftercare services include the full gamut of therapeutic means, short of part time or full time hospitalization. The availability of these services has been particularly helpful when a patient discharged from the Aftercare Clinic is in need of further help and returns to the clinic. Recently we have also

TABLE I
Patient Population of Psychiatric Aftercare Clinic 1959-1965

	1959	1960	1961	1962	1963	1964	1965
Census January 1	42	53	60	58	77	178	272
New admissions	45	36	32	46	152	211	181
Readmissions	13	19	11	19	31	23	19
Total admissions	58	55	43	64	183	234	200
Cases closed	47	48	45	45	82	140	224

On January 1, 1966 the census of patients in the clinics was 248.

opened an evening extension of the Aftercare Clinic, to take care of patients who in the course of their recovery and rehabilitation have taken on full-time jobs or other daytime responsibilities and are unable to come during the day.

When a patient is in need of help, one month, one year or ten years after discharge, he returns to the Aftercare Clinic. Although the clinic is part of the OPD, it can be said that he returns to the in-patient/out-patient complex which aftercare represents. The institutional transference is immediately operative and the patient can receive help as soon as contact with the Aftercare Clinic is renewed. As a matter of fact, there is evidence that during difficult times his knowledge that if things get "really bad" he can return to the clinic for help, may be instrumental in overcoming whatever difficulty he is facing. If and when he does return to the Aftercare Clinic, a short period of treatment and care is usually all that is needed before the patient can again be discharged.

A couple of years ago we asked the question: If the ties to the hospital are as significant as described above, if the transference to a service, clinic, institution can have healing and even preventive effects, could we not discharge our patients much sooner, once a functional improvement had been reached? This approach has been tried over the past year, with promising results (Table I).

For the first time we have been able to check the increase in the number of

patients. January 1, 1966 we had 24 fewer patients than January 1, 1965. Note the sharp increase of cases closed, from 140 in 1964 to 224 in 1965. The most remarkable statistic, however, is that the number of readmissions did not increase with the accelerated closing rate as we thought it might. There was actually a slight decrease. It must be kept in mind that this result concerns only one year (1965) and more time is needed to confirm or disprove our hypothesis that institutional transference, the knowledge that help is available if and when needed, has therapeutic and preventive effects on the aftercare patient living in the home community.

In terms of the concept of institutional transference and the philosophy of "once an aftercare patient always an aftercare patient," it becomes apparent that the Aftercare Clinic is a constant observance facility that deals with the continuum of health and illness in an individual who has once been an in-patient in a psychiatric department of a general hospital. We use the terms health and sickness in their functional meaning. By health we mean homeostatic psychic equilibrium particular to each individual, which enables him to function and derive pleasure. By sickness we mean a disturbance of this equilibrium with concomitant inability to function and derive pleasure. Successful treatment usually means a return to status quo ante.

With these somewhat simplified definitions in mind, it seems that the aftercare patient has achieved through the Aftercare Clinic a relationship that denotes continuity in health and disease, a knowledge and even an acceptance of what is healthy and what is sick, and of what to do when symptoms of sickness make their appearance. The Aftercare Clinic maintains a fluidity of movement for the psychiatric patient. He functions in the home and community. When his symptoms begin to reappear he returns to the Aftercare Clinic. With some restorative therapy the patient is again discharged and able to maintain function. The need for readmission as an in-patient is greatly diminished as a result of the services of Aftercare Clinic.

I emphasize the functional approach because this has been the traditional approach of medicine to illness. No one attempted plastic heart valves and arteries or artificial kidneys until very recently, when, through scientific and technological advances these became possible. Yet, attempts at reconstructive psychotherapy followed as soon as Freud formulated his theory of human behavior. There is a great deal to be learned from the application of psychodynamics to reparative and restorative techniques of therapy, before psychiatric reconstructive measures can be more successfully applied. It seems that psychiatry has been deprived of a most valuable phase of seeing and understanding function in its adaptive manifestations, before embarking on effecting deep personality changes, a form of treatment which always connotes going against rather than with nature. The psychoanalytic model is still too often sought, while the importance of the restorative psychotherapeutic model is underestimated. This attitude is often due to insufficient understanding of what each implies; it certainly underestimates how difficult it is to achieve a significant personality

change. The idea of making or remaking man has always been exciting; learning how to live with man as he is seems to have little appeal.

The functional approach has another advantage. It permits us to define more accurately what is sickness and what is health, particularly the latter. With an operational definition of health as the goal to strive for in the management of the patient, we are less likely to get lost in vague corrective psychotherapeutic aims while unwittingly fostering dependent and regressive needs of the patient. Techniques permitting regression may be the mainstay of reconstructive therapy; in the functional approach, however, we try to weaken the natural tendency to regress, so prevalent in every sick person, as soon as possible and by whatever means available. In part, illness in general and psychiatric illness in particular may be viewed as a need to regress. Keeping this in mind, and fully respecting the patient's need, regression should be kept to a minimum because of its frequently egosyntonic characteristics. The atrophying aspects of regression are well known. A broken arm needs rest in a cast for reunion of the broken parts. However, as soon as reunion takes place, passive and active exercise of pertinent muscles is imperative to prevent atrophy and ankylosis.

The need to regress is certainly present in aftercare patients. The initial regression which required the in-patient admission is an indication to the therapist that this is a form of adaptation this individual uses when confronted with overwhelming life circumstances. We can perform an important therapeutic task by gauging the patient's need for regression, the degree to which it needs to be satisfied and when it is to be interrupted. As a rule the patient will give us clues which when properly interpreted, will help us to gauge his regressive needs. Function and regression, then, are part of the same process and are important facets of what we term health and sickness. The aftercare patient permits us to study and follow his cycles of health and illness, to develop skills with which to treat them successfully, with or without rehospitalization and hopefully to develop techniques which will reduce the need for rehospitalization.

As I have indicated before, it is my contention that the aftercare patient has one foot in the hospital and the other in the community. Thus far my discussion has been centered on the traditional approach to aftercare as care that emanates from and is bound to the hospital. It has also been brought out that this approach emphasized the patient as an individual, and, although the help of relatives was enlisted in the totality of treatment of the patient, it was patient centered. The therapeutic endeavor consisted of attempts at modifying the patient. The same applies to the functional approach to treatment. What is being called for recently in addition to the patient centered approach is the community centered approach. The former deals with the medical model and the latter with the social model. The comprehensive approach would combine the virtues of both models, "... one that addresses the problems of changing basic conditions of living and at the same time makes provisions to help individuals become capable of taking advantage of the changed conditions and opportunities." (6)

Assuming that the community centered (social) approach which concerns itself with changing basic conditions of living through social reform is tried out

and adopted, it is doubtful as to whether it will be in the hands of the psychiatrist or in the hands of a team of which the psychiatrist will be a member. In either event, the social model requires a great deal of preparation, planning and testing, and under the best of circumstances is some time distant. Certain measures concerning the patient in the community and pertaining to the medical model for which the psychiatrist has been trained and in which he is knowledgeable, are available right now. Quality of care which has too often signified effort in depth can also stand for effort in breadth. We can contribute as much by paying more attention to the family and other significant individuals in the patient's life as we can by trying to modify the patient. Recovery and maintenance of function can more readily be achieved by greater knowledge of the family and its dynamics with appropriate intervention directed at key individuals than by concentrating solely upon the patient. With the aftercare patient's ties to the hospital fully operative, the way is clear to an approach to the family for study, diagnosis and therapeutic measures. Several steps are felt to be immediately available and can be undertaken without undue strain on the resources of the Aftercare Clinic.

1. *Expanding the role of the caseworker.* Upon the patient's admission to the Aftercare Clinic the family constellation will be reviewed. Interest will be shown not only in the immediate relative but also in more distant members of the family who have important emotional ties with the patient, and even friends; interviews with these will be suggested during which dynamics of the relationships will be studied. Eventually a dynamic diagnosis of the whole family will be established. In planning for treatment, casework therapy as well as psychiatric treatment will be considered. Certain key members of the family will be selected for therapy and emphasis will be placed as much upon the individual and his problems as on the aftercare patient himself. What is suggested here is influencing significant people in the patient's environment as much as possible in terms of their dealing with their own difficulties. This in turn will positively influence our initial patient. Before or concomitantly with an attack on mental illness by the social approach a more immediate and concentrated attack using the family circle as the base is suggested. The caseworker becomes a central figure in this effort, while the psychiatrist leads and coordinates the entire operation.

2. *Expanding the role of the psychiatrist.* It is anticipated that in the course of the caseworker's contacts with the different relatives there will be an increased need for psychiatric consultation. The Aftercare Clinic will provide it, and, whenever psychiatric treatment of relatives is necessary, it is suggested that this be done in the Aftercare Clinic (in the past the relative was referred to a different clinic for psychiatric treatment). Occasionally joint sessions of patient, relative or relatives, caseworker and therapist will be called. The rationale for this concentration of services is both administrative and therapeutic. Not only do we wish to be able to move with speed and under unified direction to act with complete knowledge of the situation from a unified record, but we also wish to preserve the basic therapeutic team of physician-caseworker acting on parallel

levels of physician-patient and caseworker-relative which has been of proven value.

The value of a single clinic treating the whole family becomes more apparent when we consider the third point.

3. *Intervention in Emergencies.* It is deemed of importance that the Aftercare Clinic stand behind its patients with its resources not only on a scheduled basis but also in emergencies. It is suggested that to the extent that resources are available, home visits be arranged by the team of therapist and caseworker. With full knowledge of the patient and the family, they are best able to evaluate the situation and to intervene appropriately.

Home visits may be utilized not only in emergencies; but in selected situations they may be scheduled to follow up a case presently in treatment or even a case that has been closed, check on the postulated psychodynamics, reevaluate the diagnosis and provide training and research opportunities.

4. *Expanding Role of the Psychologist.* A wider function for the psychologist is suggested, not only as a psychodiagnostician, but in the area of his relationship with the therapist. It is felt that the role of the psychologist is often not sufficiently understood and therefore not sufficiently appreciated by the resident-therapist. On the other hand, the psychologist has little opportunity to see how his work is utilized by the therapist in the course of therapy. Individual sessions between psychologist, the resident, and his supervisor will take place periodically. The patient will be discussed from the viewpoint of his psychological tests and the clinical picture. The psychologist will have the opportunity to follow the clinical progress of the patient, while the resident will have a practical lesson in psychodiagnostics demonstrable on his own patient. This may be a step in the direction of the psychologist becoming the diagnostic "road-mapper." (7)

Parts of this plan have been tried on trial basis. We have several active family treatment cases and at least one situation of extended practical cooperation between resident and psychologist. These modest attempts have met with great interest on the part of those concerned and are of promising nature.

SUMMARY

Aftercare in this department of psychiatry has been practiced according to the traditional medical model of helping the patient to change from a condition of predominant sickness to a condition of predominant health. Transference to an individual and to the hospital has been the basic principle followed. A feeling has been nurtured in the patient that help will be available to him any time he may need it in the future. When he needs help and requests it, we use all therapeutic modalities available, priority being given to psychotherapy and drugs. The emphasis has been on the individual patient.

Recently, what has been emphasized as the aftercare goal is the patient's return to function in the family and community. A further enlargement of the scope of aftercare is suggested with the aim of including the whole family as the object of treatment and care. This may be a necessary intermediary step, still within the medical model, and preliminary to the broader social model of dealing

with whole communities. Aftercare may have a special role to play in the gradual process of uniting the individual-centered approach with the emerging social-centered approach.

By combining the characteristics of in-patient and out-patient care, aftercare may be the predecessor to longitudinal psychiatric approach to the individual wherein mental health will be practiced preventively and therapeutically on an out-patient basis, requiring only the briefest in-patient stay on special occasions. Aftercare offers laboratory-type conditions for the intensive study of comprehensive mental health in a small segment of a community population which has one factor in common, namely an in-patient admission to a psychiatric department of a general hospital.

Finally, it is hoped that aftercare may be instrumental in bridging the artificial and unnecessary dichotomy between in-patient and out-patient services.

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Senile Arthrosis of the Knee Joint: Degenerative Osteoarthritis

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Multitissue degeneration of the components of the knee joint is among the common disabling skeletal lesions of the aged. Generically it is the local manifestation of degenerative osteoarthritis affecting the articulations of most of the skeleton, but in the knee joint in elderly individuals it presents a syndrome far more crippling and in its advanced stages more destructive than when found in other joints. It is invariably bilateral although often the presenting complaint is more severe in one knee.

The intensity of symptoms or the degree of functional impairment appears to bear little relationship to the extent of tissue degeneration. Symptoms may appear within days or weeks even though the process has been developing for months or years. Clinical experience has shown that once the aged knee joint becomes symptomatic it remains so. Given proper rest and palliative treatment the disability may be partially ameliorated. The intensity of the pain will vary but the remissions and exacerbations continue to worsen.

Unlike similar processes in the vertebral column, senile arthrosis of the knee appears earlier, more severe, and far more frequently in elderly females than males (1). In the course of many years (2) I have never seen the process so severe or disabling to an elderly male as to warrant surgical intervention whereas it is not uncommon in female patients. While this is an expression of personal judgment since others may recommend surgery in cases with less deterioration, it is also a measure of relative severity of the process in the two sexes.

This clinical judgment finds support in related episodes. The degree of degeneration seen in the knees of patients of comparable age that have been explored for other reasons, for example the repair of fractured patellae not uncommon in the elderly, differs notably in the sex of the patient. The hypertrophy of the synovial tissues, jellied and fibrotic (as compared to the florid appearance of more acute synovitis in younger age groups) is almost always greater in the elderly female. The expanse of degeneration of articular cartilage and menisci is also greater. An exception is the advanced degeneration found in later years in the traumatized knee joints of former contact sport athletes, especially long-term football players. The elderly males referred to in this comparison were not of that special group.

The cause of this sex linked difference in senile arthrosis of the joint is not as yet apparent. It is most certainly not related to previous years of active or conversely years of sedentary living. The most severe cases in the writer's experience represented dramatic extremes. One was a woman, past 60 years of age, who had worked as a cook for 40 years. The other was a woman who had never been en-

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gaged in strenuous work. Both were treated surgically at The Mount Sinai Hospital. In short, clinical observation has not as yet established the nature of this aspect of the etiology of degenerative arthrosis of the knee joint (See Bauer et al (3) for experimental observations of the knees of rabbits).

One factor that appears to be related to the severity of the lesion is obesity. Most though not all of women whose severe disability has merited surgical con-



FIG. 1. Localized chondromalacia patellae. Appears after 30 years of age in over 80% of knee joints. A prodromal degeneration.

sideration have been obese. Equally obese males with similarly affected knee joint, even though repeatedly requiring treatment, do not approach the same degree of functional impairment. The influence of sex hormones in this regard has been tangentially suggested.

Degenerative arthrosis of knee joint is the most frequent clinical impairment of this process of all the appendicular joints of the human skeleton. It is second only to spondylopathy. Although articular degeneration can occur in all joints its presence is not always apparent. The explanation is not difficult to understand. Physiologically the human knee joint permits only a restricted range and direction of motion; it is not nearly as universal a joint as the shoulder or hip.

It is direct weight-bearing at a contrived angle in the sagittal plane due to the varus slant of the femora. The cartilaginous weight-bearing surfaces are cushioned by a vestigial mechanism, a pair of fibro-cartilaginous menisci much thinner and of less surface area than the menisci of anthropoids. There is but small surface area in the femoral condyles to receive any immediate force. Its lateral



FIG. 2. X-ray film shows advanced osteoarthritic changes. Open joint showed massive synovial hypertrophy and widespread chondronecrosis of femoral condyles and patella and advanced degeneration of menisci. Medial meniscal space is almost obliterated.

protections are ligamentous. There is no bony socket as the acetabulum of the hip, and no bony mortise as the malleoli of the ankle joint. It is not relieved by gravitational pull in the orthograde position as are the joints of the upper extremity. In brief the human knee joint is a badly contrived mechanism subject to multiple malevolent effects of a lifetime of weight bearing.

The pathologic changes in the deterioration of the articular tissues are well known. In over 80 per cent of knee joints in patients over 30 years of age there is increasing degeneration of the patellar articular cartilage (Fig 1) (4). The

inflammatory processes which gave the lesion its older name osteoarthritis are secondary to the degenerative changes and are probably reactions to the localized trauma of movement along irregular surfaces or to pressure on softening areas. The primary degenerations of articular cartilages, menisci, synovia and intra-articular ligaments are cellular and chemical.

The gross pathology in advanced cases is of importance to the clinical findings. Synovial hypertrophy can develop to the point where a joint is almost full of tissue (Fig 2). Extensive chondromalacia with perichondromatous osteophytes may be seen in cases of recent onset of symptoms. The crucial ligaments are at times deteriorated to threads and in some instances have lost their insertions. The menisci are thinned (5), often shredded in part or entirely. Usually the open joint has the appearance of interstitial avascularity rather than that of engorgement as seen in other synovial lesions. The impression is of a completely worn mechanism and one wonders how the individual could have borne weight on it at all.

The above description is of the extreme type of case that warrants surgical intervention. Cases that are observed in arthrotomies performed for other reasons appear less severe but we know (6) must also be advancing. This leads to the chief puzzle of the clinical problem. Except in the most advanced cases, the degree of degeneration as seen by exploration or by x-ray appears to bear little relation to the degree of functional impairment or pain. Further, one wonders why pain and impairment varies from day to day or from season to season, why one may find less pain in a joint more deteriorated than in one less deteriorated or why the contrary may be true.

It is probable though not demonstrable that pain is related to secondary intrinsic traumatic synovitis rather than to the degeneration, and therapy directed to the secondary inflammation is the palliative (7). This accounts for relief being obtained by rest or by any anti-inflammatory therapy in all but the most advanced cases. In the latter, pain may be aggravated by pressure from edematous, swollen, greatly hypertrophied masses of synovial tissues. In these instances arthrotomy and debridement is indicated for selected cases (8).

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RADIOLOGICAL NOTES

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CASE NO. 276

A 34 year old woman was admitted to the hospital because of intractable diarrhea containing blood and mucus. She had noted frequent bowel movements for many years, but these were easily controllable until two years prior to the present admission. At that time, roentgen and proctoscopic diagnosis of familial polyposis had been made and the patient was advised to undergo total colectomy. This was refused until the recent exacerbation of lower bowel symptoms. Family history was relevant in that the father had familial polyposis and had died from a massive rectal hemorrhage.

Examination revealed a pallid, obese woman with physical findings normal. Except for microcytic anemia with hemoglobin value 9.5 gm/100 cc, the laboratory findings were normal. Barium enema revealed the colon to be normally distensible with preservation of the normal haustral pattern (Fig 1A). Innumerable small and medium sized intraluminal filling defects were noted, some with distinct short pedicles and others with broad bases (Fig 1B). The colon was not shortened and the terminal ileum appeared normal. The rectum was involved in the same process as the remainder of the colon. This fact was confirmed at sigmoidoscopy, where numerous adenomatous polyps were encountered.

The patient was explored and subtotal colectomy and ileoproctostomy performed. The patient did not consent to total colectomy and permanent ileostomy. The pathologic specimen confirmed the diagnosis of familial polyposis. There was one small adenocarcinoma in the descending colon without evidence of metastases; the remainder of the polypoid lesions represented adenomatous polyps.

DISCUSSION

Familial intestinal polyposis is a hereditary disease transmitted by a dominant gene. It usually becomes symptomatic in the second or third decade and is a premalignant condition with carcinomas usually developing about ten years after onset of symptoms. It may be associated with soft tissue or bone tumors (Gardner Syndrome) or other independent tumors such as brain neoplasms (Tureot Syndrome). Radiologically, the polyps are usually easily identified and are distributed throughout the colon including the rectum. Occasionally, the polyps are distributed segmentally, mainly on the left side. The bowel usually preserves normal distensibility, with no roentgen evidence of inflammation, although pathologically inflammatory changes can be identified. Carcinomas may be seen either as single or multiple lesions. The main differential diagnosis includes ulcerative colitis with pseudopolyp formation and lymphosarcoma. In colitis, the bowel is usually shortened with loss of normal haustration, with or

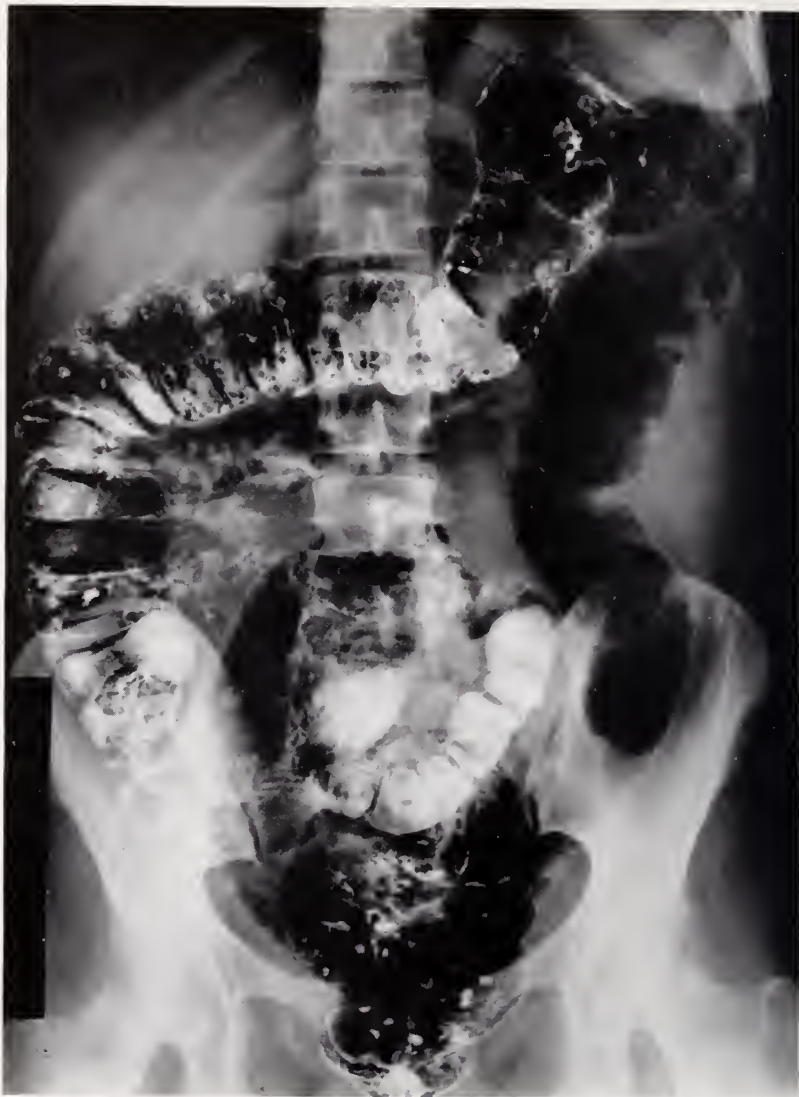
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Case 276. Fig. 1A. Barium filled colon reveals normal distensibility and normal haustrations throughout large intestine. There is no shortening of bowel. Numerous small and medium sized intraluminal filling defects can be seen throughout colon, including rectum. There is no evidence of hypersecretion or irritability.

without ulcerations. The polypoid lesions of lymphosarcoma are usually nodular and irregular with distorted mucosal folds (1). The treatment of choice is total colectomy.

Case Report: FAMILIAL POLYPOSIS.



Case 276. Fig. 1B. Double contrast study confirms presence of numerous intraluminal polypoid filling defects noted in barium filled bowel. Distensibility is normal.

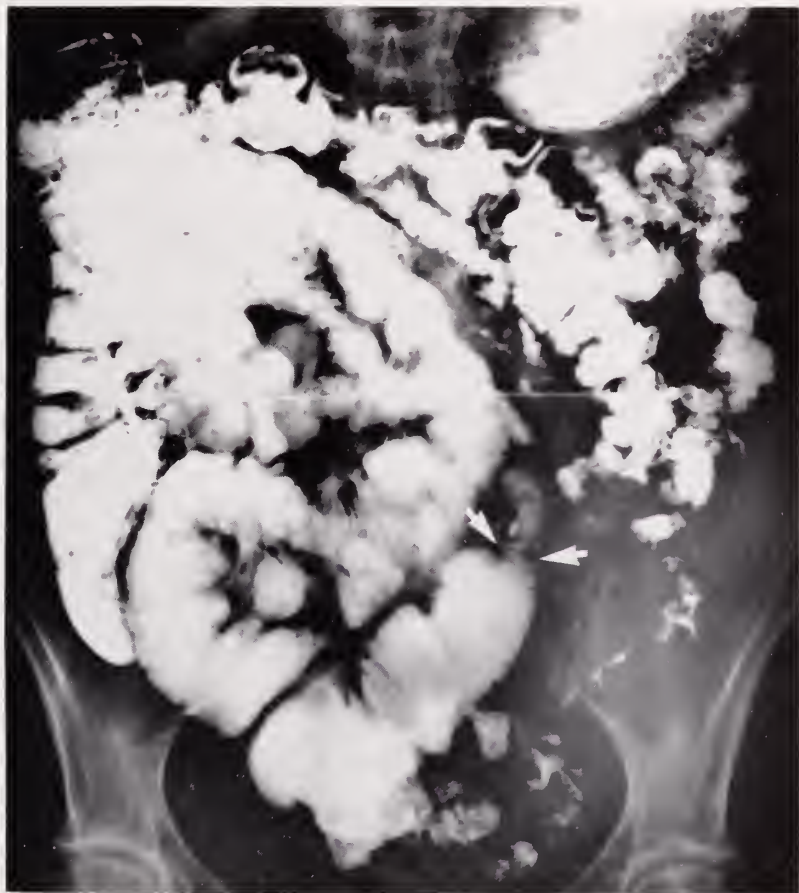
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CASE NO. 277

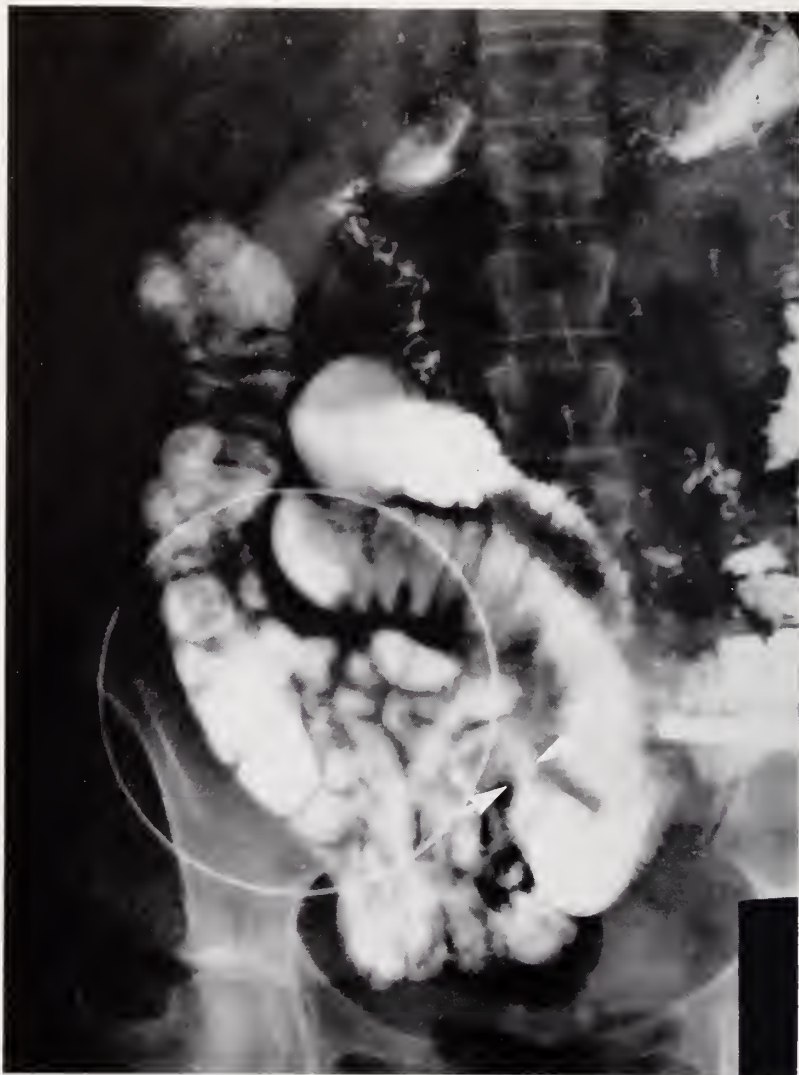
A 44 year old woman was admitted to the hospital with one week history of abdominal pain and swelling. There was no associated vomiting, anorexia or

icterus. The patient had been in good health except for mild hypertension. On careful questioning, the patient stated that she had taken Esidrix (hydrochlorothiazide and potassium chloride) daily for ten days before the onset of abdominal symptoms.



Case 277. Fig. 1A. Small bowel examination reveals dilated loops of jejunum and proximal ileum. Dilated ileum ends are tapered, smooth, concentric (between arrows). No associated ulcerations or masses are seen. Stenotic segment is short. Bowel immediately adjacent appears intrinsically normal.

Obstructive series performed the day of admission revealed dilated small bowel loops suggesting low mechanical small bowel obstruction. A small amount of gas and feces were noted within the colon. Barium enema was found to be normal. A small bowel series showed moderately dilated loops of jejunum and proximal ileum. There was a localized area of tapered concentric narrowing in the distal ileum with an abrupt transition to normal caliber in the distal ileum



Case 277. Fig. 1B. Smooth conical narrowing is again seen (*between arrows*). The lesion is noted in a different location in relation to the abdominal cavity than in Fig. 1A indicating lack of fixation.

(Fig 1A, 1B). The contours of the narrowed segment were smooth and no associated masses or ulcerations were seen.

At laparotomy, a localized stenotic segment was identified in the distal ileum. This was resected and end-to-end ileoileal anastomosis was performed. The local lymph nodes appeared soft and slightly enlarged. Pathologically, a shallow ulceration with surrounding acute inflammation was found in the center of the resected specimen. The area of stenosis was the seat of non-specific subacute fibrosing inflammation within the submucosa, muscularis and mesenteric fat

tissue. The lymph nodes showed acute and subacute inflammatory changes. The patient tolerated the operation well and made an uneventful recovery.

DISCUSSION

The association of small bowel obstruction and prior ingestion of potassium containing Thiazides (1) is well recognized. Radiologically, the stenotic segment is usually short and solitary, located in the distal ileum. On rare occasion multiple segments of narrowing have been seen. The obstruction is often incomplete and rarely is associated mucosal ulceration noted. Ulcerations are frequently identified on the pathologic specimen (2). It is often difficult to demonstrate the stenotic segment, since it shifts place within the abdomen during the examination. The lack of fixation of the narrowed segment of small bowel helps differentiate this entity from obstruction due to adhesion, where the bowel is fixed around the band. The pathogenesis of the inflammatory stenosis is not clear, but is thought to be related to the rapid and localized discharge of potassium chloride from the enteric coated pill. The Thiazide-potassium small bowel strictures must also be differentiated from stenoses of the small bowel due to vascular compromise, whose lesions are usually longer and with prominent mucosal thickening and distortion. In neoplastic stenotic lesions such as primary carcinoma, Hodgkin's Disease or metastatic carcinoma, the associated masses, nodular contours, ulcerations and eccentric lumen are usually easily identified.

Case Report: THIAZIDE-POTASSIUM CHLORIDE ILEAL STENOSIS.

ACKNOWLEDGMENT

The editors wish to thank Dr. Samuel K. Elster and Dr. Arthur H. Aufses, Jr. for permission to publish this case.

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CASE NO. 278

A 60 year old man was examined because of abdominal pain and rectal bleeding. Barium enema performed ten years earlier had revealed a slightly lobulated mass in the rectum. It measured 3 by 2 cm diameter and was situated on the right lateral wall of the rectum (Fig 1). It had a broad base and fine corrugations were noted on the surface. At that time no therapy was instituted and the patient was lost to follow-up. Proctoscopic findings at the present examination revealed a large polypoid mass on the right lateral rectal wall, three inches from the anal verge. Barium enema now showed a large sessile mass 4.5 by 3.5 cm in the location noted ten years previously (Fig 2). The characteristic "soap bubble" surface

was well demonstrated. The patient was admitted to the hospital and the lesion was removed by multiple sigmoidoscopic fulgurations. All tissue thus removed failed to show malignant changes. Repeat barium enema after fulguration revealed a normal rectum (Fig 3).



Case 278. Fig. 1. Barium enema reveals slightly lobulated intraluminal mass on right lateral rectal wall (between arrows). It is sessile and measures 3 x 2 cm diameter. The surface is slightly irregular.

DISCUSSION

Villous adenomas occur with great frequency within the rectum. When small they are usually asymptomatic, but when they attain large size they may cause a change in bowel habits, tenesmus and mucous pseudodiarrhea with or without electrolyte imbalance. The case presented demonstrates that these benign tumors are extremely slow growing neoplasms and that when properly fulgurated, they can be totally removed (1). It must not be forgotten that when the villous tumor is large, carcinomatous changes may be found near its center, thus multiple biopsies should be performed prior to fulguration.

The roentgen appearance is typical when the rectal tumors are large. They are sessile and sharply margined from the adjacent normal rectal wall. When



Case 278. Fig. 2. Repeat examination ten years later again reveals broad base lobulated mass in a similar position (between arrows). It now measures 4.5 x 3.5 cm diameter. The barium coating its surface imparts fine cobblestone pattern.

studied by double contrast method, the barium coating the tumor reveals a fine to coarse surface pattern imparting a velvety or "soap bubble" appearance.

Case Report: RECTAL VILLOUS ADENOMA—TEN YEAR FOLLOW-UP.

ACKNOWLEDGMENT

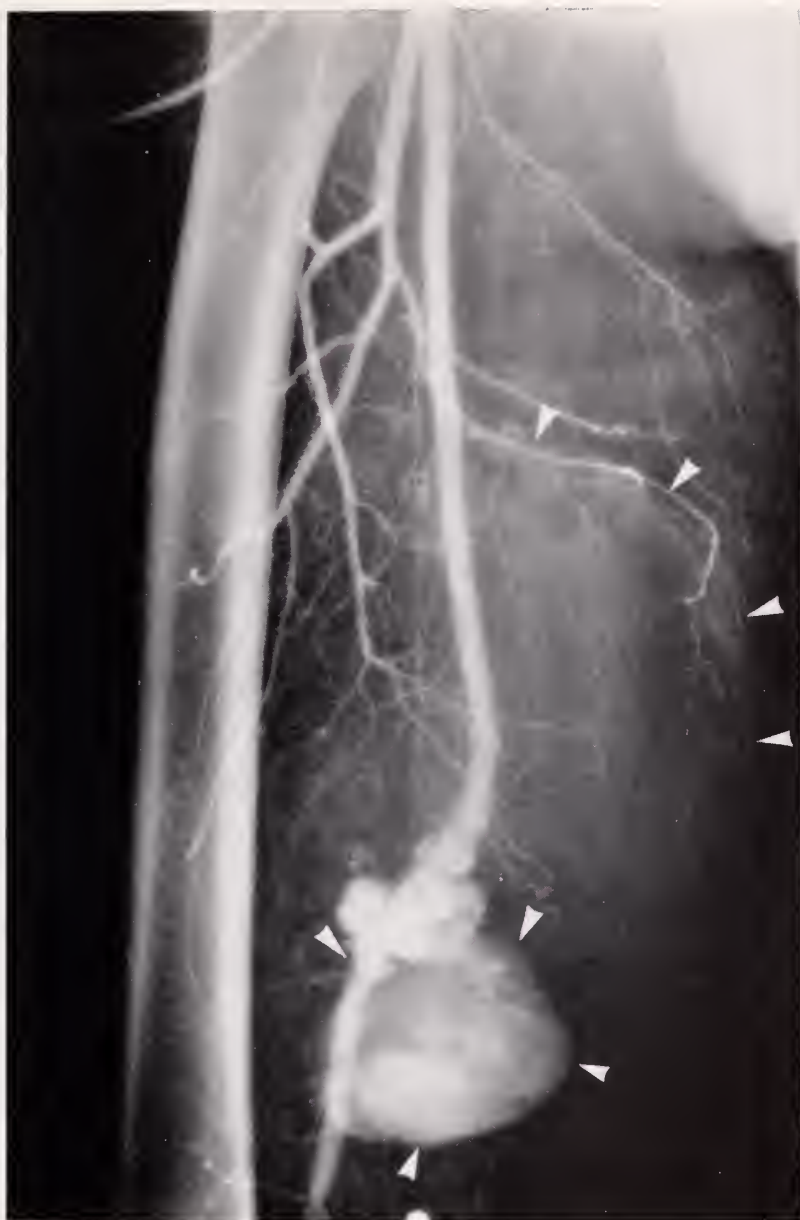
The Editors wish to thank Dr. Robert Turell for permission to publish this case.



Case 278. Fig. 3. Three months later. Repeat examination after fulguration reveals entirely normal rectum.

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Case 279. Fig. 1. Percutaneous femoral arteriography reveals lobulated aneurysmal sacculcation of superficial femoral artery (*between arrows*) at level of distal third of the thigh. There is, in addition, evidence of large soft tissue mass medial to femur, measuring 12 x 15 cm. This is outlined by small vessels (*along upper arrows*). No premature venous filling or tumor stains are seen.

CASE NO. 279

A 69 year old man was admitted to the hospital because of marked swelling of the right thigh and calf noted several weeks after mild local trauma. Physical examination revealed a large non-tender brawny slightly pulsatile mass in the posteromedial aspect of the thigh. A to-and-fro bruit was audible by auscultation over the right femoral artery. The right thigh measured 22 cm diameter, compared to 17 cm on the left. Radiographic examination of the thigh revealed a normal femur. A large soft tissue mass was identifiable medial to the bone. There were no abnormal calcifications within this mass and the tissue planes were intact. A percutaneous right femoral arteriogram was then performed which revealed a large lobulated smooth saccular aneurysm at the distal third of the femoral artery (Fig 1, *lower arrows*). A large mass was outlined by numerous displaced and stretched branch vessels medial and superior to the aneurysm (*upper arrows*). No tumor stain or premature filling of veins was noted. Surgery was performed in an attempt to remove the aneurysm and graft the femoral artery. Pathological examination of the removed portion of the artery revealed the vessel to be surrounded by and infiltrated by rhabdomyosarcoma.

DISCUSSION

This case is of interest in that the saccular femoral aneurysm demonstrated on arteriography was not the cause of the patient's problem, but the result of the adjacent soft tissue sarcoma. Most descriptions of arteriograph findings in peripheral soft tissue sarcoma fail to describe aneurysm formation as the result of direct vessel wall invasion, and instead merely mention tumor stain, vessel displacement and other classical signs of a malignant tumor bed. Therefore the association of a large soft tissue mass with an adjacent aneurysm noted during peripheral arteriography should suggest the possibility of soft tissue sarcoma with arterial invasion.

Case Report: RHABDOMYOSARCOMA WITH RESULTING ANEURYSM OF SUPERFICIAL FEMORAL ARTERY.

ACKNOWLEDGMENT

The editors wish to thank Dr. Lester Blum, Dr. Milton Mendlowitz, and Dr. Robert L. Wolf for permission to publish this case.

CLINICO-PATHOLOGICAL CONFERENCE

Purpuric Rash and Pancytopenia in an Elderly Female

Edited by

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A 71 year old white housewife was admitted to The Mount Sinai Hospital with a purpuric eruption of two weeks duration.

She had noted progressive weakness and anorexia for three months and had lost twenty-five pounds in weight. Two weeks prior to admission, she suddenly developed pruritic, reddish-purple macules and papules involving the entire body, including the mucous membranes. The lesions gradually faded; however, she developed a productive cough, shortness of breath and evening temperature elevations to 105F. The day of admission she had shaking chill and substernal pain.

She suffered from intermittent pain in both knees and ankles for thirty years and examination four years prior to admission revealed mild deformities consistent with osteoarthritis. A latex fixation test was negative. Fifteen years earlier the patient had developed urticaria following a penicillin injection. There was no history of ingestion of drugs or toxins and no previous hemorrhagic manifestations.

She was acutely ill and tachypneic. The blood pressure was 124/60, pulse rate 120/min., respiration 32/min. and temperature 104.2F. There were purpuric macules on both lower extremities. Other fading lesions were noted over the abdomen, trunk, upper extremities and mucous membranes of the mouth. The heart was normal. Crepitant rales were present bilaterally in both lung bases posteriorly. The spleen was palpated three fingerbreadths below the left costal margin. No other significant abnormalities were noted. The hemoglobin was 12.2 gm/100 cc. The white blood count ranged between 1890 and 3200/cu mm with a shift to the left. The sedimentation rate was 25 mm/hr. The peripheral smear showed some hypochromia, anisocytosis and an occasional giant platelet. The platelet count was 42,000/cu mm and the reticulocyte count was 0.6 per cent. The urine was normal. Bleeding, clotting, and prothrombin time and a Rumple-Leed test were normal. Blood urea nitrogen, uric acid, calcium, phosphorus, fasting blood sugar and serum electrolytes were within normal limits. The serum albumin was 2.8 gm/100 cc and globulin 2.8 gm/100 cc. Serum mucoproteins and acid precipitable globulin values were elevated. Zinc sulfate turbidity was 1.7 units (normal 4.8 units). Serum haptoglobins were 40 gm/100 cc. Gamma and nongamma Coombs test, lupus preparations and blood serology were negative. No hemosiderin was present in the urine. A tuberculin test (intermediate strength) and febrile agglutinins were negative. Bone marrow examination revealed marked erythroid hyperplasia. Megakaryocyte production was adequate

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and no abnormal cells were reported. Chest x-ray showed bilateral infiltrations in the lower lobes and a suggestive density in the right hilum. An electrocardiogram revealed Q waves in leads 3 and AVF.

The patient was given gamma globulin and placed on erythromycin and tetracycline therapy. However, she continued to do poorly and had temperature elevations to 104F. Multiple blood cultures were sterile. Leukopenia and thrombocytopenia as low as 20,000/cu mm persisted. The hemoglobin level fell to 9.8 gm/100 cc. Prednisone and isoniazid therapy were instituted. A punch biopsy of one of the skin lesions was reported as showing chronic nonspecific inflammation. On the eighth hospital day the patient was unresponsive and diaphoretic with blood pressure of 80/50 and pulse of 80 beats/min. The electrocardiogram was unchanged. Despite vasopressors, the addition of colimycin, chloramphenicol and intravenous hydrocortisone, she died three hours later.

*Dr. Victor Herbert:** Prior to the acute onset of the pruritic, reddish-purple maculo-papular eruption, this elderly lady had progressive weakness and anorexia and a twenty-five pound weight loss, suggesting some underlying chronic disease. Her acute illness resembled vascular purpura, since the usual hemorrhagic purpuras are generally petechial. Vascular or anaphylactoid purpuras are urticarial and represent one of the few situations in which the purpura is maculo-papular rather than just macular.

Therefore, she had a chronic illness on which an acute vascular anaphylactoid type purpura was suddenly superimposed. What can produce such a purpura? She had no history of ingestion of drugs or toxins. Bacterial or viral infections may be responsible and on day of admission, she did have a shaking chill with substernal pain, a cough productive of whitish sputum and a temperature elevation to 105F. On admission, there was a slight reduction in the red count, a marked reduction in the white blood cell and platelet counts, and splenomegaly. The peripheral blood smear showed only some hypochromia, anisocytosis and an occasional giant platelet. The differential white blood count revealed 74 per cent polymorphonuclear leukocytes with a shift to the left, so the patient did have an acute infectious process and was able to respond by producing leukocytes. We still have to explain the splenomegaly and the leukopenia rather than leukocytosis. The Rumphe-Leed test was normal. However, some patients with vascular purpura do have a negative Rumphe-Leeds test and the test may be negative with a platelet count well below 50,000/cu mm. The total serum globulin was at the lower limit of normal or perhaps slightly reduced, with the gamma globulin definitely reduced.

This patient had hypogammaglobulinemia, pancytopenia, infection and splenomegaly. Such a combination suggests a lymphoproliferative disorder or multiple myeloma. Although electrophoresis of the serum was not performed, the serum mucoprotein and acid precipitable globulins were elevated and explain why, despite the low gamma globulin level, the total globulin value was normal. The serum haptoglobin values were low and the patient did have falling hemoglobin level during hospitalization suggesting a mild hemolytic anemia,

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although no hemosiderin was present in the urine. The persistent fever and chest x-ray examination which showed "bilateral lower lobe infiltrations and a density in the right hilar region" is consistent with a bilateral pneumonia although lymphomatous infiltrations cannot be excluded. Let us assume she had a bacterial infection which was present from the onset of her disease three months before admission. We would have to consider tuberculosis, or possibly an acute bacterial infection superimposed on tuberculosis, in view of the history of daily temperature elevations. Weakness, anorexia, fever and weight loss in addition to the lower white count suggest tuberculosis. If she had tuberculosis, the tuberculin test should have been positive although anergy occurs in acute tuberculosis or during reactivation of chronic tuberculosis which becomes fulminant. However, I do not think tuberculosis was the underlying disease. More likely she had an underlying lymphoproliferative disorder since patients with such disorders have not only hypogammaglobulinemia, but increased susceptibility to infection and frequently anergy when seriously ill. The bone marrow examination was not helpful since the marked erythroid hyperplasia was probably a response to low grade hemolysis. The normal number of megakaryocytes in conjunction with the low platelet count again makes one think that the low platelet count was due to a failure of platelet release, as may be associated with malignancies of the blood such as the lymphoproliferative disorders. Did she perhaps have a myeloproliferative disorder? Generally these patients do not have low gamma globulin values. For the same reason, lupus erythematosus would be unlikely.

Clinically, the patient had a lymphoma. Superimposed on this lymphoma was hypogammaglobulinemia and an infection, possibly tuberculosis but more likely pneumococcal or staphylococcal. Disturbing about this case is the lack of renal involvement. Allergic or anaphylactoid purpuras are classically associated with renal damage and hematuria. Although the urine specimen was normal at the time of admission, she came to the hospital two weeks after the onset of the purpura. Unfortunately, there was no urinalysis performed at the time when abnormalities would have been most likely. During hospitalization, there was a small amount of protein in urine and an occasional red and white cell, which may or may not have been significant. In any case, if renal lesions had been present, the patient was markedly improved since the blood urea nitrogen level was normal.

Vascular purpuras involve many systems and, in fact, cases with anaphylactoid vascular purpura have had myocardial involvement consisting of a diffuse angitis involving the small blood vessels. The electrocardiogram showed Q waves in leads 3 and AVF, which may be significant.

The patient was given gamma globulin because of the hypogammaglobulinemia, and erythromycin and tetracycline in the hope that she had a bacterial infection. The leukopenia thrombocytopenia and anemia persisted and she had occasional guaiac positive stools, suggesting a Henoch-Schoenlein purpura (anaphylactoid vascular purpura involving the gastrointestinal tract). A punch biopsy of the skin was not helpful. It showed chronic nonspecific inflammation and findings consistent with an anaphylactoid vascular purpura.

In summary this patient presented with a three month history of progressive illness with weakness, anorexia and weight loss. The underlying lesion was probably a lymphoma; or one of the lymphoproliferative disorders. Chronic lymphatic leukemia is unlikely because the white cell differential showed only 20 per cent leukocytes without abnormal lymphocytes and monocytes. Superimposed was an infectious process, hypogammaglobulinemia and an anaphylactoid type of vascular purpura. The mechanism of the purpura is unclear, although one speculation is that bacterial antigens stimulate antibodies which react with the vessel walls and produce an acute vascular purpura ten days or two weeks later.

Question: How often are vascular purpuras associated with thrombocytopenia?

Dr. Herbert: Rarely! However, I thought the patient had an underlying lymphoma which would explain the thrombocytopenia.

Question: How often are vascular purpuras associated with a low gamma globulin?

Dr. Herbert: The gamma globulin is usually normal, but again patients with lymphomas frequently have a low gamma globulin.

Question: How often is pruritus present with purpura?

Dr. Herbert: Stefanini and Dameshek state: "Pruritus is common in Henoch-Schoenlein purpura."

Question: In the protocol, it was stated that the skin lesions were macular and papular. However, in the physical examination, the skin lesions were described as macular which would be consistent with a thrombocytopenic type of purpura.

Dr. Herbert: I would assume that if this were a vascular purpura with a maculopapular eruption, then the papules should have completely resolved shortly after they occurred and macular lesions would be found two weeks later. I am inclined to think that the thrombocytopenia was not idiopathic because the patient would probably have had ecchymosis and petechiae.

Question: Do you think that the low gamma globulin adequately explains the apparent inability of the red cells to sediment in the presence of what would be an overwhelming infection, or did she have hypofibrinogenemia?

Dr. Herbert: I think the patient very possibly did have hypofibrinogenemia. One aspect of the case that I did not discuss was the possibility of hepatic involvement. The enlarged liver could have explained the mucoprotein elevation which classically occurs in liver disease. Lymphomatous involvement of the liver may result in hypofibrinogenemia and defects in glycoprotein production.

Question: Do you think the patient had meningococemia?

Dr. Herbert: If the patient were younger, I would have thought more seriously of a meningococemia. I rejected this because the onset of the purpura antedated her admission and the purpura of meningococemia is usually petechial in nature. In addition if she had a meningococemic purpura associated with a Waterhouse-Friedrickson syndrome, I would have expected an earlier demise.

*Dr. Koffler:** At autopsy, the patient had multiple purpuric lesions over both upper extremities, chest and abdomen. The heart was not enlarged and, micro-

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scopically, there were multiple areas of cellular infiltration associated with degeneration of myocardial fibers (Fig 1). In some areas, there was a marked degeneration of muscle fibers with fibrosis. Several small organized thrombi were present in the arteries of the heart. In perivascular regions and throughout the interstitium of the heart, there were infiltrations of small histiocytic type cells,

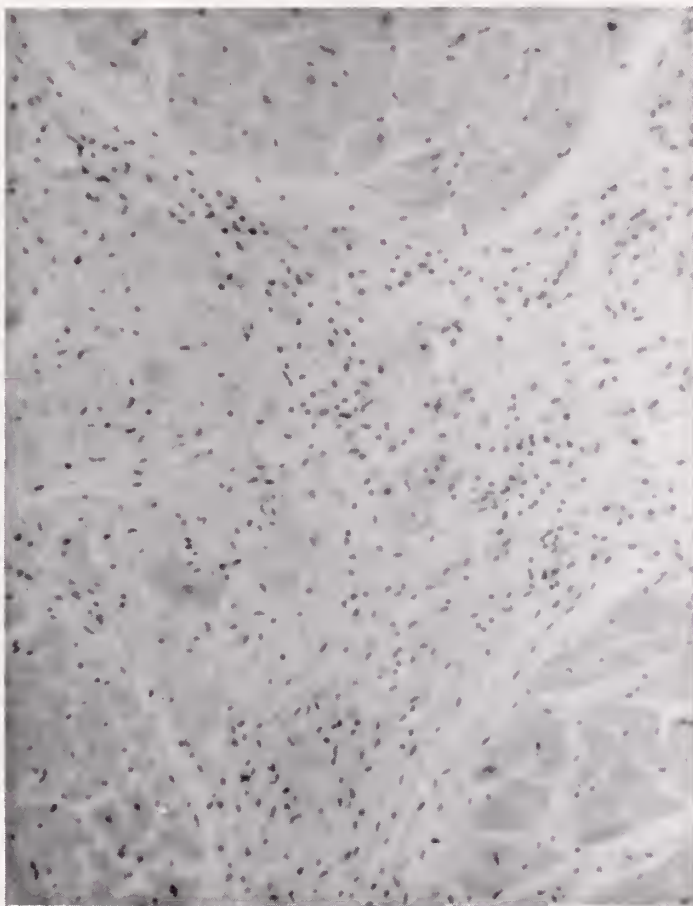


FIG. 1. Infiltration of myocardium by mononuclear cells and degeneration of myocardial fibers (H & E $\times 100$).

which had pale, eosinophilic cytoplasm and small dark nuclei. These cells stained with special stains for glycoprotein (Fig 2). In the infiltrates were found numerous mast cells which showed the typical metachromatic granules when stained with toluidine blue. In some areas there were nodular aggregates of Anitschkow's cells. Therefore, the heart presented a rather confusing diagnostic picture of histiocytic infiltration, mast cells and lymphocytes associated with destruction of myocardial fibers.

The lungs were slightly enlarged and some areas were hypocrepitant, espe-

cially the lower lobes. There were wedge shaped pale areas throughout the lower lobes of both lungs. We can assume these were responsible for the densities apparent in the x-rays. The hilar lymph nodes were bilaterally enlarged, but showed no infiltration by tumor cells. The overlying pleura contained granulation tissue which was also infiltrated by numerous histiocytic cells, lymphocytes, and mast

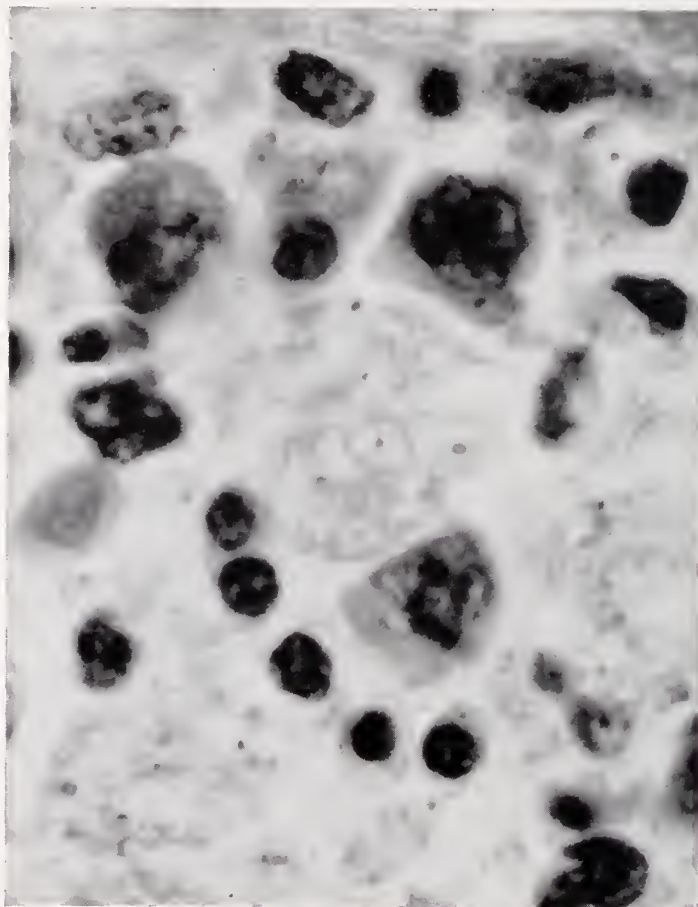


FIG. 2. Myocardial infiltration by Periodic Acid Schiff positive histiocytic cells (PAS $\times 400$).

cells. The lung showed extensive interstitial fibrosis, prominent in the consolidated areas. Microscopically, the lining cells of the alveoli were hyperplastic, and many alveoli showed bronchialization. Lymphocytes and cells characterized by dense, somewhat marginated chromatin along the nuclear membrane and eosinophilic cytoplasm, resembling prohistiocytic cells, as well as cells with a more eosinophilic cytoplasm and small nuclei characteristic of histiocytic cells were found.

The liver was enlarged and the cut surface was pale and tannish in appearance.

Microscopically, the centrilobular areas were necrotic; most probably a terminal phenomenon related to shock. However, in many portal areas there were lymphocytes, histiocytic and large prohistiocytic cells associated with some fibrosis. The spleen was enlarged and the cut surface was soft and diffuent. Microscopically, the architecture was markedly distorted and in some areas there were only

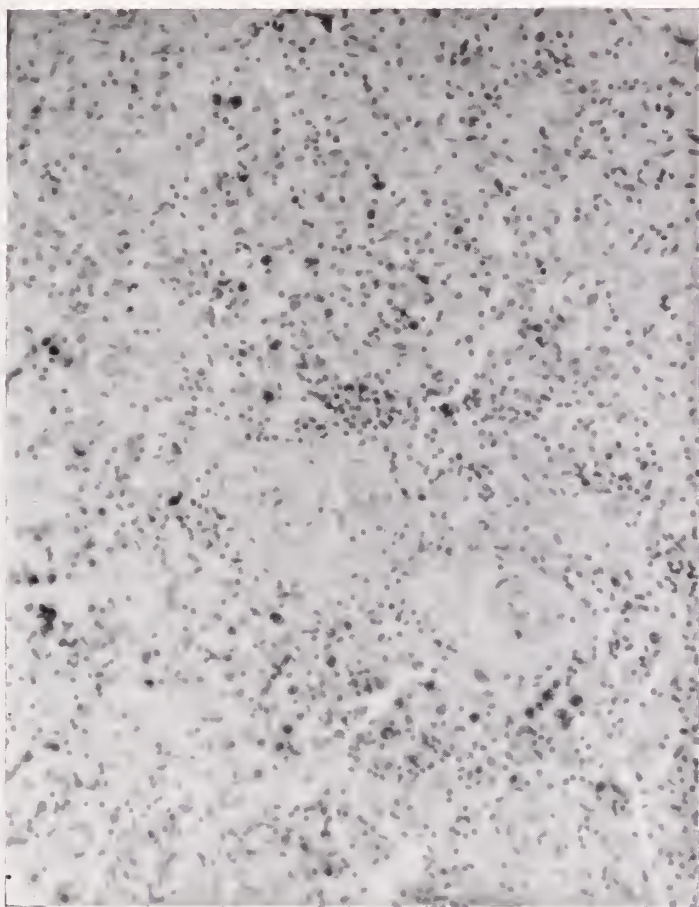


FIG. 3. Destruction of splenic architecture and infiltration by abnormal mononuclear cells (H & E $\times 100$).

remnants of follicles with germinal centers (Fig 3). The sinusoids were packed with large foamy looking histiocytes, numerous prohistiocytic cells and lymphocytes (Fig 4). Some follicles were completely replaced with this type of infiltration and no Reed-Sternberg cells were evident. The prohistiocytic cells were similar to those in the liver and lung. In addition, the large histiocytic cells contained erythrocytes. In some areas the erythrocytes were intact, perhaps freshly phagocytized and very active erythrophagocytosis was present throughout the spleen. There was a moderate amount of iron in the spleen and relatively little

iron in the bone marrow and lymph nodes. The bone marrow sections at autopsy revealed the marrow to be moderately hyperplastic with foci of erythroid hyperplasia and erythrophagocytosis. Infiltrates of histiocytic and prohistiocytic cells, quite similar to those seen in the liver, the spleen and the lymph nodes, were found to contain ghost of erythrocytes and partially digested erythrocytes (Fig

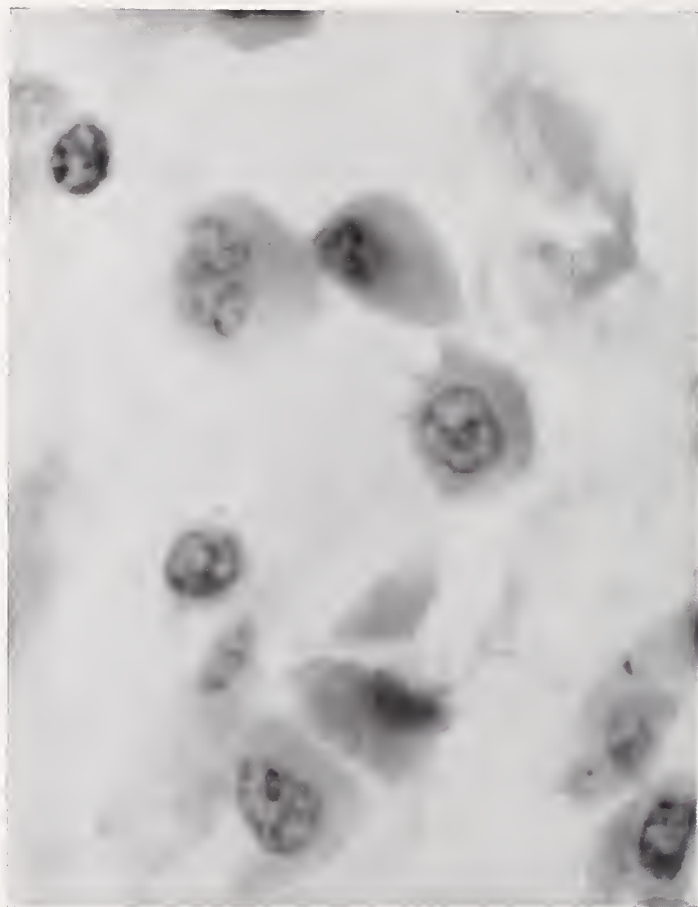


FIG. 4. Atypical prohistiocytic type cells and histiocytes packed with ghosts of red blood cells within spleen (H & E $\times 400$).

5). The lymph nodes showed histiocytic cells of the type found in the heart. The abdominal, mesenteric and hilar lymph nodes showed similar infiltrates.

The kidneys revealed only nephrosclerosis. Infiltrations of histiocytes were not found, but abnormal prohistiocytic cells were seen in the glomerular capillaries.

The adrenal gland showed an infiltration of prohistiocytic cells associated with lipid depletion and some cortical atrophy. Therefore, all the features of histiocytic medullary reticulosis were observed. No Reed-Sternberg cells were present

and fibrosis or necrosis was not present in the spleen, lymph nodes or bone marrow. Fibrosis was present only in the heart and lungs. It has not been agreed to consider histiocytic medullary reticulosis as a type of lymphoproliferative disorder. Pathologically, it is classified between the lipid histiocytosis and the malignant lymphomas. The infiltrate of histiocytic medullary reticulosis has

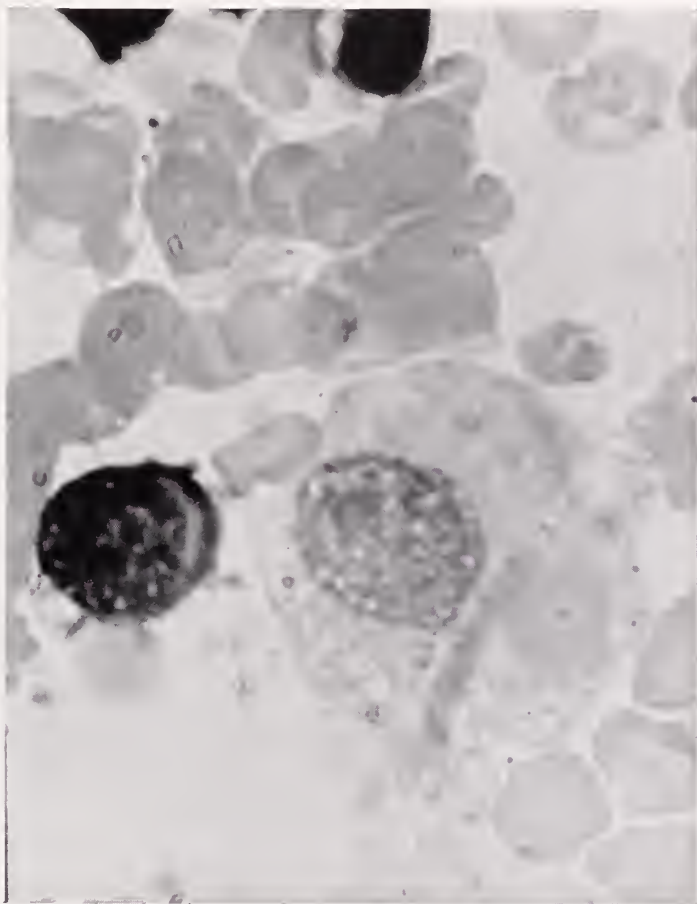


FIG. 5. Large reticulum cell within bone marrow containing an engulfed erythrocyte (Wright stain $\times 950$).

features similar to Letterer-Siwe disease where only mature histiocytes are present. On the other hand, there are features of Hodgkin's disease and many have considered these cases to be an atypical form of the latter. However, the prohistiocytes which are characteristic of medullary reticulosis are not present in Hodgkin's disease. Fibrosis and tissue necrosis is also characteristic of Hodgkin's disease. Erythrophagocytosis is diagnostic of medullary reticulosis, whereas it is not usually present in significant degree in Hodgkin's disease. The survival of the patients with histiocytic medullary reticulosis is considerably less than in

Hodgkin's disease. Therefore, I think there are sufficient differences both from the clinical and from the pathological viewpoint to classify medullary reticulosis as a separate entity.

Question: Are the skin lesions related to the disease?

Dr. Koffler: In the present case, the skin lesions showed only chronic nonspecific inflammation without evidence of histiocytic medullary reticulosis. However, a case with abnormal histiocytes in the skin has been reported.

Question: I am aware that many accept histiocytic medullary reticulosis as a disease entity. I have been hesitant in accepting it since the diagnosis is based on the presence of histiocytes and erythrophagocytosis.

Dr. Koffler: I agree. However, there is value in differentiating it from both the clinical and pathologic standpoint. Certainly erythrophagocytosis is present in many diseases, but in Hodgkin's disease massive erythrophagocytosis in association with a histiocytic infiltrate is not found. Also, the mature type of histiocytes that diffusely infiltrate the various organs is not seen in Hodgkin's disease. Whether or not it is truly a distinctive entity from an etiologic standpoint, one cannot say. In addition to the distinctive clinical and pathological features, the patients are remarkably unresponsive to any form of treatment, unlike patients with Hodgkin's disease or lymphosarcomas.

Final diagnosis:

1. Histiocytic Medullary Reticulosis involving heart, lung, liver, spleen, adrenal glands, lymph nodes, and bone marrow
2. Nephrosclerosis

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The Muscle Biopsy Program at Mount Sinai Hospital: Results of a Five Year Prospective Study*†

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"Therefore I begged Professor Billroth to recover a small piece from the muscle by direct incision. We selected the Deltoides on the left side since this muscle felt very thick and was almost completely without function. This minor operation was performed on the 15th of August (1864). After application of chloroform to the neck and upper half of the breast, the skin acquired a deep rose color. The panniculus overlying the muscle was at least 1 cm. thick. The muscle on its surface and in its deeper exposed layers was pale, yellowish-white and offered no resistance to the incision of the knife. A pea-sized piece was removed and examined by Professors Billroth and Frey with a variety of preparation methods."

Griesinger, 1865 (1)

"Moreover, a great advance has been made in the pathological anatomy of this disease by the impulse given to it by Griesinger, who, with the assistance of Billroth, ventured to excise a portion of the deltoid muscle of a little boy in order to make an histological examination of it..."

Duchenne, 1868 (2)

The formal study of muscle pathology in the living patient began, appropriately, with the first muscle biopsy obtained by Griesinger from a 13 year old boy with the classic manifestations of pseudohypertrophic muscular dystrophy (Fig 1). The histological discovery of muscle fiber replacement by fat and connective tissue in this biopsy (Fig 2) resolved the clinical paradox first observed some years previously by Duchenne: the coexistence of paralysis and "muscular hypertrophy" in dystrophic patients.

A century of study since then has greatly refined the surgical pathology of most organ systems, but the pathology of muscle has advanced but a short distance from its purely descriptive origins. One must admit, in agreement with Greenfield, that the principal difficulty has been "the lack of precise definitions of fundamental histological alterations in muscle."

A second obstacle has been the deficiency of broad-based clinical studies of patients with a variety of neuromuscular disorders. The accumulation of case reports cannot substitute for this because the study of the isolated case at best, provides only one reference point in the natural history of the disease.

The lack of a uniform clinical classification, based preferably on the inferred site of anatomical dysfunction, makes it difficult to uncover pathogenetic factors and to compare observations from one clinic to another.

Finally, our inability to apply the more sophisticated details of muscle

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physiology to the problems of pathologic interpretation has prevented the formulation of a general theory of pathophysiology applicable to muscle as a tissue.

In these areas of difficulty, progress has been most satisfying with the last, where the direct application of electrophysiological, histochemical, biochemical, and electronmicroscopic techniques has at least permitted the sketching of blueprints for the basic structure and function of the muscle fiber. Much of this knowledge remains disconnected, however, because of our inability to extrapolate it to the bedside.

To some extent our appreciation of neuromuscular disorders has been dulled by a tendency to discuss them with vocabulary that is a confusing blend of clinical and pathological terms. Investigators who insist that all of their patients with myositis must exhibit skin abnormalities, tender muscles, proximal weakness, elevated creatine phosphokinase levels, and muscle biopsies with necrotic fibers overrun by inflammatory cells will be able to report a high incidence of convincing cases from their clinics. On the other side, they will probably gain no new insights with this approach and they may suffer considerable discomfort in attempting to classify two additional and contradictory groups of cases: those with similar clinical syndromes but without inflamed muscles and those with inflamed muscles but without the anticipated clinical syndrome.

The problem, in short, is to identify and define the structural changes in muscle produced by disease and to objectively record the medical biography of the affected patient. These efforts must be parallel and independent. Considerable experience in this problem has been acquired by several groups of investigators whose works have now become standards of reference and excellence. Adams, Denny-Brown and Pearson (3) have given us an expanded view of the entire field. Greenfield, Shy, Alvord, and Berg (4) recognizing the need for strict classification of the pathologic changes encountered in muscle biopsies, produced a monograph that is distinguished by its objective approach. The increasing number of topical reviews and specialized symposia devoted to muscle diseases is a measure of the seriousness of this problem (5-17).

Nevertheless, satisfactory integration of clinical and pathological observations has seldom been achieved because of the frequent necessity for retrospective evaluation of clinical documents that have not been uniformly recorded. Furthermore, the clinical classification is frequently unclear because of the admixture of anatomic, physiologic, and biochemical criteria employed in the diagnostic formulation. Ideally, the classification of neuromuscular disorders should imply an anatomically-linked substrate based on the concept of diseases of spinal cord, peripheral nerve, and muscle. Numerous disorders cannot be so simply classified, however, because of overlapping dysfunction in several anatomic areas. These examples of "mixed disease," in which combinations of cord and root dysfunction or peripheral nerve and muscle dysfunction exist, may also be expected to impose a variation on the pattern

of pathologic change in muscle. Interpretation of the pathologic anatomy in these conditions requires careful separation of the primary and secondary factors that produce structural changes in this system.

This has led us to explore the problem from both a clinico-pathological and experimental standpoint, the latter supplementing the former. The results of a five year study designed to independently record clinical and pathological data obtained from patients with neuromuscular disorders constitute the substance of this report.

MATERIAL AND METHODS

Several preliminary phases of investigation were pursued before the present program was established.

Ten Year Review of Previous Muscle Biopsies (1949-1958)

There were 187 muscle biopsies submitted to the neuropathology laboratory for study during this period. Retrospective review of the microscopic slides disclosed that a definitive diagnosis could not be made on most of this material and none were satisfactory for detailed structural study. The principal defects were attributable to inadequate sampling, faulty fixation, and improper microtomy. Review of the clinical records of these patients also yielded little useful information because of inconsistent recording of data, conflicting observations, and incomplete diagnostic impressions. It was apparent, nevertheless, that a frequent source of error was performance of biopsy on clinically uninvolved muscles or on muscles whose advanced state of dysfunction precluded recognition of the disease pattern.

Two Year Pilot Study (1959-1960)

During this period, the study of 58 biopsies enabled us to establish liaison with interested surgical and medical specialists, devise a clinical protocol, standardize the technic of biopsy, perfect the necessary histological, histochemical, and electronmicroscopic methods, and design a system for data recording and retrieval.

Five Year Prospective Study (1961-1965)

The present report is based on the prospective study of 484 muscle biopsies obtained from 348 patients with various neuromuscular disorders that were examined during this interval. Technically unsatisfactory biopsies and patients with inadequate clinical documentation were excluded. The team of investigators included one neurologist and two neuropathologists.

Population

The age at the time of biopsy ranged from 3 months to 88 years. The mean age was 44.8 years and 42% of the biopsies were obtained from the 40 to 60 year age group. The female/male ratio was 1:2. The originating services included the Departments of Medicine, Neurology, Surgery, and Pediatrics.

Clinical Data

History, physical examination, and neurologic status were recorded by the neurologist. Reexaminations and changes in status were recorded throughout the period of hospitalization. Members of the patient's family were interviewed to document the family history. When indicated, examination and laboratory tests were performed on relatives. Urinalysis, blood count, routine clinical chemistries, blood serology, and spinal fluid analysis were obtained on all patients. Special clinical chemistry determinations included studies of creatine-creatinine excretion, serum electrophoresis, liver function, and serum enzymes (glutamic-oxalacetic and glutamic-pyruvic transaminase, creatine phosphokinase and lactic dehydrogenase). Appropriate radiologic studies were also obtained. Electromyography was performed by the Division of Clinical Neurophysiology of the Department of Neurology. In selected cases biochemical studies were performed on serum and muscle homogenates by the Division of Neurochemistry of the Department of Neurology. These studies included determinations of oxidative, hydrolytic, and transferring enzyme activities and various intermediate metabolic products in muscle. Additional special studies included urinary gonadotrophin titer, 17-ketosteroids and 17-hydroxycorticoids, seminal fluid analysis, and skin biopsy for sex chromatin analysis performed by the Division of Endocrinology of the Department of Medicine. Urinary aminoacid chromatography was performed by the Clinical Research Center.

The clinical diagnosis was based on the history and physical examination with patients classified into groups according to anatomic localization of the disease (18). When possible on purely clinical grounds, further subclassification was made, such as in cases of myopathies with positive family histories and the typical progression and pattern of involvement of one of the muscular dystrophies. Except for myotonic dystrophy, with its distinctive clinical picture, no attempt was made to further subclassify the dystrophies. Patients with myopathies in whom muscle pain or tenderness was a prominent symptom or finding were classified as "myositis" regardless of etiologic considerations, since although the biopsy may occasionally show a specific causative organism, the clinical syndrome of idiopathic myositis does not differ according to our criteria from one due to specific infection. All other cases of myopathy not showing the distinctive clinical features of dystrophy or myositis, were classified as "other myopathies." As in all clinical groups, associated illnesses were independently recorded but were not included in the clinical diagnostic category.

In the neurogenic disorders, the categories used included myelopathies (with subclassification of amyotrophic lateral sclerosis for patients showing the complete syndrome), peripheral neuropathies (including radiculopathies), and an additional group for patients showing both spinal cord and root or peripheral nerve disease who were classified as myeloneuropathies. In addition, patients with weakness due to cerebral or brainstem disease were classified as "encephalopathies with neuromuscular dysfunction."

Additional major categories included diseases of neuromuscular transmission (myasthenia gravis and other myasthenic syndromes) and diseases of unknown anatomic basis, such as the floppy infant syndrome in which it is not possible clinically to localize the process to nerve or muscle. Finally, muscle biopsies were performed on a large group of patients with no neuromuscular syndrome to exclude or establish the diagnosis of a variety of systemic diseases that might affect muscle (eg arteritis). These were classified as "No Neuromuscular Syndrome." The clinical categories can be summarized as follows:

- A. Myopathic Disorders
 - 1. Muscular dystrophy (without myotonia)
 - 2. Myotonic dystrophy
 - 3. Other myotonic syndromes
 - 4. Myositis
 - 5. Other myopathies
- B. Neurogenic Disorders
 - 1. Amyotrophic lateral sclerosis
 - 2. Myelopathies of other type
 - 3. Peripheral neuropathy
 - 4. Myeloneuropathy
 - 5. Charcot-Marie-Tooth disease
 - 6. Guillain-Barré syndrome
 - 7. Werdnig-Hoffmann syndrome
 - 8. Encephalopathies with neuromuscular dysfunction
- C. Myasthenic Syndromes
 - 1. Myasthenia gravis
 - 2. Other myasthenic syndromes
- D. Disorders of Unknown Anatomic Basis
 - 1. Floppy infant syndrome
- E. No Neuromuscular Syndrome

Muscle Biopsy

The sites of biopsy were designated by the neurologist guided by the clinical data. In most cases an attempt was made to obtain two (occasionally three) biopsies from different sites. These sites exhibited different degrees of clinical disability and represented either proximal and distal muscles or muscles from both upper and lower extremities. Biopsies were performed as scheduled operative procedures in the operating room by neurosurgeons or general surgeons who had been oriented to the special problems of the biopsy technique. Local anesthesia was produced by infiltration of the skin (but not of underlying muscle) with Xylocaine. Electrical stimulation was used to localize nerve endings in an effort to obtain motor endplates in the biopsy. Muscle was excised by sharp dissection, initially in parallel to the longitudinal axis of the muscle fibers and finally by cross incision and undercutting. The minimal sample was 2.5 cm long, 1 cm wide, and 1 cm deep. The biopsy was

then placed in gauze moistened by cold isotonic saline prior to further processing. Samples of skin and, in some cases, segments of peripheral nerve were included. Samples for electronmicroscopy were separately incised after clamping in situ with a modified muscle clamp (19). These samples were immediately placed in osmium tetroxide or glutaraldehyde.

Pathological Studies

The processing and evaluation of muscle biopsies were performed in the Division of Neuropathology. Biopsies were received in the operating room directly from the surgeon and the tissue was separated for low temperature quenching and for fixation in various fixatives.

Histopathology

Muscle samples were rapidly dissected into 2 to 3 cm long strips. Each end was ligated with suture and the strip was pulled through a glass tube 1 cm in diameter. The ends of the sutures were tied to impose a slight stretch on the muscle strip and to prevent contraction artifact during fixation (Fig 3, 4). The specimens were immersed in Bouin's solution, fixed for 18 to 24 hours, washed for 24 hours, dehydrated in graded alcohols, infiltrated with paraffin (58°C MP), and embedded for sectioning in longitudinal and transverse planes. Paraffin sections of 2μ to 6μ thickness were stained with Ehrlich's hematoxylin and eosin, Gomori's trichrome technique, and Mallory's phosphotungstic acid hematoxylin technique. An average of 4 blocks of longitudinal and 6 blocks of cross-sectional orientation were prepared from each muscle.

Histochemistry

Separate strips of muscle, similarly stretched, were quenched in 2-methylbutane cooled to -190°C in liquid nitrogen for preparation of cryostat sections (Fig 5-9). These were incubated for carbohydrate and protein reactive groups and for various enzyme activities including α -glycerol phosphate, succinic, lactic, malic, isocitric, and β -hydroxybutyric dehydrogenases, DPN and TPN-linked diaphorases, cytochrome oxidase, phosphorylase, adenosine triphosphatase, acid and alkaline phosphatases, nonspecific esterase and acetylcholinesterase according to methods cited by Barka and Anderson (20). Formalin fixed frozen sections were used for demonstration of the terminal intramuscular axons by a modified Bielschowsky procedure and for visualization of the motor end-plates (21).

Electronmicroscopy. In selected cases, samples for electronmicroscopy were fixed in phosphate buffered osmium tetroxide or 4% glutaraldehyde for 30 to 60 minutes. The latter were washed briefly in isotonic sucrose, post-treated with osmium tetroxide, and embedded in Epon-812 after alcoholic dehydration. Ultrathin sections were prepared with a Porter-Blum MT-2 Ultramicrotome using a diamond knife. Uranyl acetate and lead-stained sections were examined in an Hitachi Model HS-7 electron microscope at 50 kv. Photographs were made on Kodak lantern slide plates or on Dupont COA7 film and developed in full strength Kodak developer D-19.

Biopsy analysis. Histopathology was evaluated by study of each structural element represented in the biopsy and was performed independently by each member of the group without knowledge of the related clinical data. The analysis included measurement of muscle fiber size and form using the method of orthogonal diameters applied to 150 to 200 fibers in cross-section (22) (Fig 10). Comparison against controls obtained from 124 normal muscles permitted quantitation of abnormally small and abnormally large fibers and an evaluation of the pattern of abnormality. Sarcoplasmic changes were classified as follows: floccular change, vacuolar change, myofibrillar condensation, basophilia, sarcoplasmic masses, collagen replacement, and phagocytosis. Abnormal fiber forms included compressed or angulated fibers, rounded fibers, ring fibers, and fiber splitting. Changes in sarcolemmal nuclei included internalization, chain formation, hyperchromatism, and vesiculation. The presence of inflammatory change, its location and distribution, and its cellular components were recorded. Changes in connective tissue and fat of the endomysium, perimysium, and epimysium were separately noted. The capsule and component fibers of muscle spindles were similarly evaluated. The myelin sheaths, axons, and endoneurium of intermuscular nerve bundles and the terminal nerve net were studied in conjunction with the motor end-plates. Arteries and veins within the muscle were examined for mural abnormalities and inflammation. Finally, the presence of microorganisms, parasites, mineral deposits, and other extraneous materials were recorded.

Histochemical preparations were similarly studied in an attempt to relate histopathologic abnormalities to structurally significant histochemical reactions, including those associated with mitochondria, lysosomes, sarcoplasmic reticulum, motor end-plates, and blood vessels. Fibers were typed, according to their pattern of oxidative enzyme activities as type I or type II, the former showing high concentrations of succinic and lactic dehydrogenases, and DPN-linked diaphorases, and the latter showing high activities of menadione-linked α -glycerophosphate dehydrogenase and phosphorylase (Fig 7, 8).

No syndrome- or etiology-oriented diagnosis was recorded in the pathology data. Instead, the principal area of pathologic change was indicated (eg atrophy, degeneration, inflammation, etc). Biopsy reports, however, were standardized to convey the main pathologic features itemized in the above categories and to include a standard diagnosis according to the following scheme:

A. Atrophy

1. Atrophy, typical of neurogenic pattern
2. Atrophy, segmental, suggestive of neurogenic pattern
3. Atrophy, unpatterned.

B. Myopathy

1. Myopathy, typical of dystrophic process
2. Myopathy, suggestive of dystrophic process
3. Myopathy, suggestive of myotonic dystrophy
4. Myopathy, necrotizing, focal or diffuse

5. Myopathy, with special histological features (glycogen accumulation, rods, etc.)
- C. Myositis
 1. Myositis, diffuse, acute, subacute, chronic
 2. Myositis, focal, perivascular or perimysial, acute, subacute, chronic
 3. Myositis, granulomatous
 4. Myositis, infectious
- D. Trauma
 1. Skeletal muscle with traumatic degeneration and repair
- E. Unknown pathologic significance
 1. Skeletal muscle with abnormal fiber form (angulation, rounding, ring fibers)
 2. Non-diagnostic (severe and advanced degeneration)
 3. Non-diagnostic (inadequate sample or technically unsatisfactory biopsy)
- F. Normal skeletal muscle

Data Recording, Retrieval, and Analysis

Both clinical and pathological data were recorded by an inverted data grouping system in which each term or characteristic was posted on a term card and the patient or case number manifesting that characteristic was punched in a meaningful position on the appropriate card (Termatrex system, Jonker Business Machines, Inc., Gaithersburg, Md.). Each term was assigned a code number and the total series of code numbers comprised the index for clinical or pathological data. An open-ended vocabulary of index terms was developed for both categories. The clinical vocabulary (including all biographical information, symptoms, physical and neurological findings, and laboratory data) consisted of 508 terms. The pathology vocabulary (including all observations of normal and abnormal structural elements in the muscle biopsy and the histochemical and electronmicroscopic data) consisted of 402 terms. Each muscle studied was assigned a separate identification number and data for that muscle were individually recorded and coded. If more than one muscle was obtained from a given patient, the corresponding clinical data were recorded in duplicate or triplicate (using the same identification numbers) to correspond with the pathology data. The term cards were designed to accommodate 10,000 case numbers and separate color-coded decks of cards were maintained for separate entry of clinical and pathological data. The average case study required the posting of approximately 70 to 80 terms in the clinical vocabulary and 65 to 75 terms in the pathology vocabulary. Case numbers were entered on appropriate term cards by means of a drill mounted on a movable carriage that could be accurately positioned for any of the 10,000 positions (Jonker 301). An illuminated view box (visual card reader, Jonker 52) was used for periodic review of data, but statistical analysis for the entire group of patients was performed with an automatic scanner and electronic totalizer (Jonker 500 scanner with model 304B totaliz-

ing counter, Computer Measurements Company). The use of this equipment permitted rapid retrieval and direct observation of possible correlations in clinical and pathological data.

RESULTS

Clinical Syndromes

The distribution of clinical diagnoses, based on the criteria previously outlined, is given in Table I. There was a broad spectrum of neuromuscular disorders including 114 myopathies, 155 neurogenic diseases, 30 myasthenic syndromes, and 5 floppy infant syndromes. There were also 44 patients with no neuromuscular syndrome.

Pathological Abnormalities

To provide a general idea of the frequency of pathologic findings in the entire patient population, each abnormality of structure will be reviewed.

a. Abnormalities of Fiber Size and Form.

The polygonal form of the muscle fiber in cross-section was best represented by measurement of orthogonal diameters. The major axis diameter was the diagonal connecting the most distant angular points in the cross-section of the fiber. The longest perpendicular offset from the major axis to the remaining angular points constituted the minor axis (Fig 10). These orthogonal diameters were proportional to the area of the fiber and their ratio was a reliable index of the shape of the fiber. The range of the smallest minor axis and largest major axis measurements encountered in 125 normal biopsies obtained from 18 different adult muscles is tabulated in Table II. Except for extrinsic eye muscles, minor axis measurements below 20μ and major axis measurements above 120μ were considered abnormally small or abnormally large respectively. The mean orthogonal diameters in the three most frequently biopsied muscles (deltoideus, vastus lateralis, and gastrocnemius) are given in Table III. The sampling of normal muscles from the pediatric population (below 15 years) was not sufficiently large to establish normal measurement limits.

Atrophic muscle fibers were encountered in 67% of cases. This was the commonest pathologic finding in the total series. Atrophic fibers were distributed in three patterns: random (78%), segmental in small groups (40%), and segmental in large groups (28%), (Fig 11, 12).

Abnormal fiber forms were also frequently observed and were classified as angulated fibers (30%), rounded fibers (38%), ring fibers (13%), and ring fibers with sarcoplasmic masses (3%), (Fig 13-16 respectively).

b. Sarcoplasmic Abnormalities.

The descriptive nature of most of the pathologic terms in current use makes it difficult to convey a precise meaning to the pathologic change that

is being observed. In spite of this, most of these terms have gained conventional acceptance and their use in muscle pathology implies an abnormality or change in state of the sarcoplasmic components. Most of the terms suggest a degenerative process which may ultimately lead to necrosis with a phagocytic response. The changes that were observed and their incidence in the patient population were as follows:

<i>Floccular Change</i>	41 %
Aggregation of sarcoplasm into a flocculent mass (Fig 17)	
<i>Vacuolar Change</i>	8 %
Formation of optically-empty vesicles of varying size (Fig 18)	
<i>Target Fibers</i>	6 %
Central clumping of myofibrils surrounded by a zone of myofibrillar loss or depletion which in turn is surrounded by a zone of normal myofibrillar pattern; in cross-section, such fibers resemble "targets" (Fig 19)	
<i>Phagocytosis</i>	35 %
Necrotic fibers containing macrophages (Fig 20)	
<i>Sarcoplasmic Basophilia</i>	
Focal zones of basophilia within fiber	30 %
Fiber splitting (longitudinal division of fibers, sometimes referred to as "budding") (Fig 21)	Less than 1 %

c. Changes in Sarcolemmal Nuclei.

Internalization, so-called migration, of sarcolemmal nuclei from their normal subsarcolemmal location to a position within the depths of the fiber was a frequent finding, occurring in 40% of cases (Fig 22).

Nuclear chain formation (a linear arrangement of closely approximated nuclei on the surface or interior of the fiber) occurred in 18% of cases (Fig 23).

Vesicular nuclei (large pale nuclei with prominent nucleoli, and thick nuclear membranes) were observed in 24% of cases and were most frequently associated with sarcoplasmic basophilia (Fig 22).

d. Inflammatory Change.

Inflammation was present in 29% of cases. Eighty percent of these were focal and 20% were diffuse of confluent in distribution. Inflammation was designated as focal (Fig 24) or diffuse (Fig 25) depending upon whether the inflammatory cell aggregates were confined to perivascular areas and perimysial septae or whether they infiltrated along endomysial lines and involved large areas of muscle fibers. The inflammatory cells were acute (polymorphonuclear leukocytes and eosinophiles) in 13% and chronic (lymphocytes, plasma cells, and histiocytes) in 87%. An infectious agent was uncovered in one case of trichinosis (Fig 26) and four cases of leprosy.

e. Connective Tissue Changes.

Increased amounts of connective tissue in the endo- and perimysium were observed in 28% of cases (Fig 27). In some cases this was associated with fatty replacement of fiber groups.

f. Muscle Spindles.

Abnormalities of the spindle capsule (dilatation or increased connective tissue) or of the muscle fiber component were observed in 24% of cases (Fig 28).

g. Intermuscular Nerves.

Intermuscular nerves were more or less randomly encountered in the muscle samples of 255 cases. Eighteen percent of these cases were classified as abnormal because of reduction in nerve fibers and increased endoneurial connective tissue (Fig 20). Visualization of the terminal nerve net by Bielschowsky silver impregnation or by methylene blue staining, although useful in the study of selected cases, did not give sufficiently reproducible results for evaluation in the entire patient group.

h. Motor End-Plates.

Motor end-plates were encountered in 40% of cases and they were considered abnormal in 38% of those cases in which they were demonstrated. Abnormality did not necessarily imply a change in size or configuration of the end-plate, since the criteria were based upon the distribution of acetylcholinesterase and nonspecific esterase in this structure. Abnormalities therefore consisted of irregular separation, distribution, or concentration of histochemically visualized enzyme reaction products. Because of the complex form of the end-plate, no satisfactory criteria for size or area were devised.

j. Blood Vessels.

Aside from perivascular inflammation (without mural involvement), the most significant blood vessel abnormality was arteritis (mural infiltration by inflammatory cells, fibrinoid necrosis, etc), but this was observed in only six cases (Fig 30).

Comparison of Clinical Syndromes and Biopsy Abnormalities

The correlation of clinical syndromes and their respective pathologic findings are given in Tables IV (fiber size and form), V (sarcoplasm and nuclei), and VI (supporting tissue, muscle spindles, and neurovascular elements). Both positive and negative trends were apparent. Taken as a group, the most frequent muscle biopsy abnormalities observed in the myopathic disorders were random atrophy, enlarged fibers, rounded fibers, floccular change, necrosis and phagocytosis, basophilia, internalized nuclei, increased connective tissue and fat, and abnormal muscle spindles. Within this group, the most distinctive pathology was observed in cases of myotonic dystrophy. In

addition to the above findings, these patients exhibited a high incidence of ring fibers with sarcoplasmic masses and sarcolemmal nuclear chain formation. The infectious myositis group included one case of trichinosis and four cases of leprosy (all of which showed myositis associated with acid-fast organisms in addition to the characteristic abnormalities of peripheral nerve).

The most significant negative trend was the lack of correlation between the muscle biopsy findings and the clinical syndrome of idiopathic polymyositis. Of 29 patients in which the clinical diagnosis was appropriate (based on the combination of fairly rapid onset of proximal weakness, pain and tenderness, dysphagia, florid dermatitis, and appropriate laboratory findings), less than 25% showed biopsy findings considered characteristic for this condition (diffuse inflammatory change, necrosis and phagocytosis, internalized nuclei with sarcoplasmic basophilia, and atrophy in segmental distribution). The lack of correlation cannot be explained by improper selection of biopsy site, since all patients had multiple biopsies of clinically involved muscle groups.

The pathologic findings in the entire group of neurogenic disorders showed a high frequency of segmental atrophy of large or small muscle fiber groups, angulated and rounded fibers, target fibers (especially in the sub-group of peripheral neuropathies), and histochemical abnormalities of the motor end-plates.

No characteristic pattern of abnormality emerged in the group of myasthenia gravis patients. Random atrophy and histochemically abnormal motor end-plates were frequent while necrosis and focal lymphocytic infiltrates were seen in approximately one-third of cases.

In two sizable clinical categories the significance of the biopsy findings remained obscure, although the trend of abnormality agreed with the general findings of their major group. The first of these was a sub-group designated *Other Myopathies*. Detailed analysis of the clinical data recorded from these 57 cases disclosed the following profile: The patients complained of limb weakness and pain of insidious onset and progressive course. Their ages at onset ranged from less than 1 year to 70 years with most cases falling in the 30 to 60 year age group. At the time of examination, their disease had been present for more than two years. There were no significant past or family histories. Concurrent systemic illnesses in this group included central nervous disease, such as seizure disorder, organic mental syndromes, etc. (5 cases), rheumatoid arthritis (6 cases), carcinoma of various organs (4 cases), diabetes (3 cases), hyperthyroidism (3 cases), scleroderma (2 cases), and polyarteritis (1 case). The most frequent findings on examination were symmetrical weakness (most pronounced proximally), atrophy of limb muscles, and depressed or absent deep tendon reflexes. The commonest laboratory abnormalities were elevated sedimentation rates and abnormal electrophoretic patterns of serum proteins, elevated transaminase (SGOT and SGPT) and creatine phosphokinase levels, and abnormal creatine-creatinine excretions. Electromyograms showed myopathic or mixed patterns in most cases but one-fourth were reported as neurogenic.

The second sub-group was *Other Myopathies*. The clinical profile of these 40 cases showed that most had presenting complaints of weakness, sensory disturbances, and wasting of insidious onset and progressive course. The age at the time of onset ranged from 10 to 70 years, but most of the cases were in the 40 to 60 year age group with a 1 to 2 year history of disability. There were no significant past or family histories. Concurrent systemic illnesses in this group included diabetes (3 cases), alcoholism (2 cases), and carcinoma (1 case). The most frequent clinical signs included symmetrical weakness, most marked distally, muscle atrophy, fasciculations, pathological reflexes, and peripheral sensory loss or sensory levels. Elevated spinal fluid protein was the most distinctive laboratory abnormality. Most of these patients had electromyograms of neurogenic pattern (although 10% were reported as myopathic) and they frequently exhibited abnormally slow conduction velocities.

Relation to Concurrent Systemic Illness

To determine possible trends in muscle pathology that might be associated with systemic illnesses, a correlation was made between pathologic findings and diabetes, thyroid disease, alcoholism, carcinoma, thymoma, history of steroid therapy, rheumatoid arthritis, scleroderma, lupus erythematosus, polyarteritis, and central nervous disease of cerebral origin. The comparison of systemic illnesses in a total of 129 patients, their associated neuromuscular syndromes, and the frequency of pathological abnormalities are presented in Tables VII, VIII, and IX.

With the exception of arteritic changes in patients with polyarteritis, no distinctive pathologic finding (or pattern) was evident for these systemic illnesses. The pathology, in point of fact, was more dependent on the presenting neuromuscular syndrome than on any of the concurrent illnesses. Furthermore, the pathologic findings in patients with neuromuscular syndromes (irrespective of the concurrent systemic illness) were in general agreement with those encountered in the entire population as summarized in Tables IV, V, and VI.

Within this group of 129 patients, normal muscle biopsies were obtained in 31 cases, 19 of which had no neuromuscular syndrome.

Relation of Clinical Signs to Muscle Fiber Abnormalities

To test the predictability of muscle biopsy abnormality from clinical findings, five common clinical signs (muscle tenderness, atrophy, fasciculations, pathological reflexes, and peripheral sensory changes) were analyzed for the related incidence of inflammation, segmental atrophy, and sarcoplasmic degeneration in the biopsies of patients that manifested these signs. The results are given in Table X. In all cases, the muscles studied were from areas directly related to the sites of clinical observation.

Muscle tenderness related equally well (somewhat less than 50%) to the presence of inflammation and sarcoplasmic degeneration in the biopsy. More than 50% of cases with muscle atrophy showed segmental atrophy and sarcoplasmic degeneration in their biopsies. Fasciculations were highly cor-

related (76%) with segmental atrophy while 53% of the cases with pathological reflexes also showed this biopsy finding. The incidence of inflammation, segmental atrophy, and sarcoplasmic degeneration in patients with peripheral sensory changes did not vary significantly from the incidence of these abnormalities in the total patient population.

DISCUSSION

To the physician in the clinic the literal message of the biopsy report carries with it an almost irresistible implication that the diagnosis is based on a reasonable integration of facts about altered form and function. But in spite of refined techniques, the abundance and accessibility of the tissue, and the relative simplicity of its structural organization, we do not yet have precise guidelines for the interpretation of muscle pathology.

During the past decade, at least 15 texts, monographs, and symposia have been published on general or specialized aspects of muscle pathology, yet remarkably few of these have been based on carefully documented and systematically recorded case material (3—17, 28). The most notable exceptions are the texts of Greenfield, Shy, Alvord, and Berg (4) (a retrospective synthesis of muscle biopsy abnormalities and clinical data from 132 patients with various neuromuscular disorders) and Walton and Adams (15) (a carefully drawn comparison of clinical histories and muscle biopsy pathology in 40 patients with myositis). Under average circumstances, however, the pathologist must still rely upon the random observations afforded him by a relatively uncontrolled muscle biopsy. Without exact observation and purposeful experimentation he can have but little insight into the developmental stages through which the structural phenomena have passed during the course of disease. This uncomfortable position was fully appreciated by Klemperer in his conclusion that "disease is the experiment of nature; we see only the results, while we are ignorant of the conditions under which the experiment has been performed."

Our ultimate purpose, then, is the formulation of pathogenesis. The present study emphasizes several conditions that must be satisfied before such formulation can be achieved.

First is the problem of classification of neuromuscular disorders. There is no general nosological agreement and current systems vary in complexity from highly simplified to elaborate (3, 5, 10, 16, 18, 23, 24, 26). Almost all systems incorporate a mixture of neurological, biochemical, electrophysiological, and pathological (even ultrastructural) criteria. Though useful for an overall concept of diseases affecting muscle, such systems are impractical at the bedside, or, worse, may lead to opinions which fluctuate "until the lab results are back." Since we wish to correlate clinical disability with structural abnormalities, the present, admittedly oversimplified, clinical scheme was adopted because it attempts only to identify the anatomical area of dysfunction (spinal cord, peripheral nerve, muscle) through the presence of measurable and unequivocal neurological signs and symptoms. The

system is flexible enough to accommodate the "unknown," "equivocal," and "mixed" cases and sufficiently elastic to permit refinement and subclassification when pathological correlation warrants this. Related to the problem of clinical classification is that of pathological diagnosis. The biopsy report too often speculates on causative factors or attempts to subclassify clinical entities. Clearly we cannot distinguish variant forms of muscular dystrophy on histological grounds without understanding their pathogenesis. Our present method of reporting is not an attempt to "diagnose." It is an attempt to systematically record (and where possible to quantitate) the individual structural abnormalities encountered in the biopsy. The principal area or pattern of pathology is then emphasized in the diagnostic impression. "Segmental atrophy, typical of neurogenic pattern" may therefore be compatible with amyotrophic lateral sclerosis, Guillain-Barré syndrome, peripheral neuropathy, or a variety of neurogenic disorders, even though subsequent longitudinal study of larger groups of cases may justify pathological subclassification.

The second condition is the controlled performance of the muscle biopsy. To minimize observational bias, clinical examination must be recorded by a properly oriented clinical group and the same ancillary tests (clinical chemistries, electromyography, radiologic studies, etc.) performed on all patients irrespective of diagnostic impression. The biopsy sites (preferably multiple) should be designated by this group and the biopsy performed by a surgeon who is aware of the requirements of the biopsy, willing to excise an adequate sample, and able to perform special techniques (eg open stimulation for motor points).

The factors requiring most control are those involving the histological preparation, beginning with excision of the muscle sample and including all stages of trimming, stretching, fixing, quenching or embedding, microtomy, and staining or histochemical visualization. The extraordinary sensitivity of muscle to improper handling is not generally recognized and the processing artifacts of muscle biopsies have rarely been described. Yet slight variation in biopsy or processing technique can easily destroy the value of an otherwise optimal clinicopathologic case study. Improper site, inadequate sample, and inattentive processing have been the principal sources of error in biopsy analysis.

Finally, the necessity to record the clinical and pathological data prospectively and independently must be stressed. The need to reduce or eliminate observational bias is obvious; the need for efficient information retrieval is less apparent. Correlation of clinical data and pathological abnormalities with the proposed system is rapid and cumulative. Data analysis can proceed in two directions: symptoms and findings to associated pathological pattern and the converse. Because the pathology data are recorded with reference to the involved cell component, structure-linked abnormalities or patterns of abnormality can be easily detected and may be useful in disclosing areas that lend themselves to experimental study (21-22, 27-32).

More important, however, is the impact of such data on the preconceptions of the pathologist. The consensus in contemporary literature, for example, is that neurogenic disorders produce segmental atrophy of muscle (circumscribed groups of small fibers) while myopathic processes give rise to sarcoplasmic changes (flocculation, nuclear internalization, basophilia, necrosis, etc.). Analysis of the patient population reported here, however, shows that almost half of those with clinical myopathy showed segmental atrophy of large or small groups and almost half of those with neurogenic disorders showed significant sarcoplasmic changes in their biopsies. The frequency of these findings in otherwise well-defined clinical groups cannot be ignored; there are obvious explanations for these discrepancies, but none has yet been strenuously tested.

Although most changes in muscle are not specific for a given disease, certain patterns and configurations of abnormalities recur with sufficient frequency to permit diagnostic classification of biopsies into general categories. These categories imply an anatomical basis for the disease process. The etiological basis can only be defined by combined clinical and pathological study.

The need for such effort was crystallized by Greenfield and his co-workers (4): "At times one wonders whether the muscle biopsy is really helpful, but this pessimistic view cannot long be maintained: one cannot help but feel that further study of more cases will disclose the answers. In this situation we have found that the microscopist should not know the clinical findings; we have repeatedly seen how difficult it is to record unbiased observations if the clinical diagnosis is known. If accurate observations can be made, recorded, carefully analysed and continuously reviewed, our present ignorance and confusion will eventually be replaced by understanding."

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TABLE I
Distribution of Clinical Syndromes

Syndrome	No. of Cases
Myopathic Disorders	
Muscular dystrophies (without myotonia).....	15
Myotonic dystrophy.....	8
Myopathies of other type.....	57
Myositis, idiopathic.....	29
Myositis, infectious.....	5
Neurogenic Disorders	
Amyotrophic lateral sclerosis.....	24
Myelopathies of other type.....	40
Peripheral neuropathy.....	63
Myeloneuropathy.....	3
Charcot-Marie-Tooth.....	
Guillain-Barré.....	3
Werdnig-Hoffmann.....	6
Encephalopathies with neuromuscular dysfunction.....	12
Disorders of Transmission	
Myasthenia gravis.....	30
Disorders of Unknown Basis	
Floppy infant syndrome.....	5
No Neuromuscular Syndrome.....	44
Total.....	348

TABLE II
Range of Orthogonal Diameters in Normal Muscle Biopsy Samples

Muscle	No. Sample	Smallest Minor Axis, range, μ	Largest Major Axis, range, μ
<i>Head and Neck</i>			
Rectus lateralis.....	1	10-20	40-60
Sternocleidomastoideus.....	2	20-30	50-80
Trapezius.....	3	20-50	60-80
<i>Trunk</i>			
Longissimus dorsi.....	4	20-40	60-80
Rectus abdominis.....	1	20-30	50-70
External intercostal.....	2	20-30	50-70
<i>Upper Extremity</i>			
Supra-infraspinatus.....	3	20-50	60-80
Pectoralis major.....	1	20-40	40-70
Deltoides.....	38	20-50	50-110
Biceps brachii.....	1	20-40	60-100
Triceps brachii.....	5	20-50	60-100
Brachioradialis.....	1	30-40	70-100
Abductor pollicis brevis.....	1	20-30	40-70
<i>Lower Extremity</i>			
Vastus lateralis.....	15	20-50	60-120
Biceps femoris.....	1	30-40	70-90
Tibialis anterior.....	2	20-40	60-90
Peroneus brevis.....	1	30-40	70-100
Gastrocnemius.....	43	20-50	50-120
Total.....	125		

TABLE III
*Mean Orthogonal Diameters of Muscles Most Frequently Biopsied**

Muscle	Sample	Minor Axis (μ)	Major Axis (μ)
Deltoides.....	38	30.23 \pm 1.07	79.50 \pm 2.02
Vastus lateralis.....	15	30.00 \pm 1.62	82.80 \pm 3.94
Gastrocnemius.....	43	30.86 \pm 0.03	80.34 \pm 2.05

* Expressed as mean of smallest minor axis or largest major axis \pm standard error of the mean.

TABLE IV
Abnormalities of Fiber Size and Form

Clinical syndrome	Cases	Atrophy, random	Atrophy, small groups	Atrophy, large groups	Abnormal large fibers	Angulated fibers	Rounded fibers	Ring fibers	With sarcoplasmic masses
<i>Myopathic Disorders</i>	(114)								
Dystrophy	15	++++	+	+	++	++	++	+	-
Myotonia dystrophica	8	++++	+	+	-	-	+++	++	++
Other myopathy	57	++++	++	+	+	++	++	+	+
Myositis, idiopathic	29	++++	+	+	-	+	+++	+	-
Myositis, infectious	5	++++	-	+	-	+	+++	-	-
<i>Neurogenic Disorders</i>	(155)								
A.L.S.	24	++	++	++	+	++	++	+	-
Other myelopathy	40	++	++	+	+	++	++	+	-
Peripheral neuropathy	63	++++	++	++	+	++	++	+	-
Myeloneuropathy	3	++++	-	-	+	++	-	-	-
Charcot-Marie-Tooth	4	++	++	++	-	+	+++	-	-
Guillain-Barré	3	-	-	++	-	-	++	-	-
Werdnig-Hoffmann	6	-	+	++	-	+	++	-	-
Encephalopathies	12	++	+	+	-	+	-	+	-
<i>Disorders of Transmission</i>	(30)								
Myasthenia Gravis	30	+++	+	+	+	+	++	+	-
<i>Disorders of Unknown Basis</i>	(5)								
Floppy infant syndrome	5	+	+	++	-	-	++	-	-
<i>No neuromuscular Syndrome</i>	(44)								
CNS disease	16	+	-	-	-	-	+	+	-
Misc. metabolic diseases	28	++	+	-	-	+	+	+	-
Total cases	348								

- = not present; + = present in less than 25%; ++ = present in 25-50%; +++ = present in 51-75%; ++++ = present in more than 75%.

TABLE V
Abnormalities of Sarcoplasm and Nuclei

Clinical syndrome	Cases	Floccular change	Vacuolar change	Target fibers	Fiber splitting	Sarco-plasmic basophilic	Phagocytosis	Internal nuclei	With chain formation	Vesicular nuclei	Focal inflammation	Diffuse inflammation	Acute inflammation	Chronic inflammation
<i>Myopathic Disorders</i>	(114)													
Dystrophy	15	++	+	-	+	++	++	++	++	++	+	+	+	+
Myotonia dystrophica	8	+++	-	-	+	+	++	++	++	++	-	-	-	-
Other myopathy	57	++	+	+	+	++	++	++	+	++	+	+	+	+
Myositis, idiopathic	29	+++	+	-	-	++	++	++	+	++	+	+	+	+
Myositis, infectious	5	++	+	+	-	++	++	++	-	-	+	-	+	+
<i>Neurogenic Disorders</i>	(155)													
A.L.S.	24	++	+	+	-	++	+	++	+	++	+	-	+	+
Other myelopathy	40	++	+	+	-	++	++	++	+	++	+	-	-	+
Peripheral neuropathy	63	+++	+	++	-	++	++	++	+	++	+	-	+	+
Myeloneuropathy	3	++	++	++	-	-	++	++	-	++	+	-	-	+
Charcot-Marie-Tooth	4	+	-	-	-	-	+	++	+	-	-	-	-	-
Guillain-Barré	3	-	-	-	-	+	+	+	-	-	-	-	-	-
Werdnig-Hoffmann	6	+	-	-	-	+	-	+	-	+	+	-	-	+
Encephalopathies	12	++	-	-	-	++	+	++	+	+	+	-	-	+
<i>Disorders of Transmission</i>	(30)													
Myasthenia Gravis	30	++	-	+	-	++	++	++	++	+	+	+	+	+
<i>Disorders of Unknown Basis</i>	(5)													
Floppy infant syndrome	5	+	-	-	-	+	+	-	-	-	+	-	-	+
<i>No Neuromuscular Syndrome</i>	(44)													
CNS disease	16	+	-	-	-	+	+	+	-	-	+	-	-	+
Misc. metabolic diseases	28	++	+	+	-	++	++	++	+	++	+	-	+	+
Total cases	348													

- = not present; + = present in less than 25%; ++ = present in 25-50%; +++ = present in 51-75%; ++++ = present in more than 75%.

TABLE VI
Abnormalities of Supporting Tissue, Spindles, and Neurovascular Elements

Clinical syndrome	Cases	Incr. connective tissue & fat	Abnormal muscle spindles	Abnormal terminal nerves	Abnormal motor end-plates	Perivascular inflammation	Arteritis
<i>Megopathic Disorders</i>	(114)						
Dystrophy	15	+++	++	+	+	-	-
Myotonia dystrophica	8	+++	+++	++	-	-	-
Other myopathy	57	++	+++	+	++	+	+
Myositis, idiopathic	29	+++	+	+	+	+	-
Myositis, infectious	5	-	+	++	-	++	-
<i>Neurogenic Disorders</i>	(155)						
A.L.S.	26	+	+	+	++	-	-
Other myelopathy	40	+	++	+	+	-	-
Peripheral neuropathy	63	++	+	++	++	+	+
Myeloneuropathy	3	++	++	-	-	-	-
Charcot-Marie-Tooth	4	+++	+	-	-	-	-
Guillain-Barré	3	-	-	-	-	-	-
Werdnig-Hoffmann	6	+++	++	++	++	-	-
Encephalopathies	12	+	+	-	-	-	-
<i>Disorders of Transmision</i>	(30)						
Myasthenia Gravis	30	+	++	+	++	+	-
<i>Disorders of Unknown Basis</i>	(5)						
Floppy infant syndrome	5	+	-	-	-	-	-
<i>No Neuromuscular Syndrome</i>	(44)						
CNS disease	16	-	-	-	-	-	-
Misc. metabolic diseases	28	-	-	-	-	+	-
Total cases	348						

- = not present; + = present in less than 25%; ++ = present in 25-50%; +++ = present in 51-75%; ++++ = present in more than 75%.

DIABETES (Total = 26)

Neuromuscular Syndrome

Dystrophy

Other myopathy

Other myelopathy

Neuropathy

Myasthenia

No N = M syndrome

THYROID DISEASES (Total = 4)

Neuromuscular Syndrome

Dystrophy

Other myopathy

ALCOHOLISM (Total = 10)

Neuromuscular Syndrome

Myositis

Other myelopathy

Neuropathy

Myelopathy & neuropathy

CARCINOMA (Total = 10)

Neuromuscular Syndrome

Myositis

Other myopathy

Other myelopathy

Neuropathy

Myasthenia

L. hemiparesis

None

THYMOMA (Total = 9)

Neuromuscular Syndrome

Myositis

Myasthenia

Cases	Atrophy, random	Atrophy, patterned	Sarcoplasmic degeneration	Necrosis	Inflammation	Incr. connective tissue & fat	Abn. inter-muscular nerves & MEP	Arteritis	Normal
2	2/2	2/2	2/2	2/2	2/2	2/2	0/2	0/2	0/2
3	1/3	0/3	1/3	1/3	2/3	1/3	0/2	0/2	0/3
3	2/3	1/3	1/3	1/3	0/3	2/3	0/3	0/3	1/3
14	11/14	8/14	7/14	6/14	3/14	5/14	2/14	0/14	1/14
1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1
3	2/3	2/3	2/3	1/3	0/3	0/3	1/3	0/3	1/3
1	1/1	1/1	1/1	1/1	0/1	1/1	0/1	0/1	0/1
3	2/3	1/3	1/3	1/3	1/3	2/3	0/3	0/3	1/3
1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1
2	1/2	1/2	2/2	1/2	1/2	0/2	1/2	0/2	0/2
6	3/6	1/6	2/6	1/6	1/6	0/6	1/6	0/6	1/6
1	1/1	0/1	1/1	1/1	0/1	0/1	0/1	0/1	0/1
1*	1/1	0/1	1/1	1/1	1/1	1/1	0/1	0/1	0/1
4	3/4	0/4	2/4	2/4	1/4	3/4	2/4	0/4	1/4
1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
1	1/1	1/1	1/1	0/1	0/1	0/1	1/1	0/1	0/1
1*	1/1	0/1	1/1	1/1	1/1	1/1	0/1	0/1	0/1
1	1/1	1/1	1/1	1/1	0/1	1/1	0/1	0/1	0/1
2	1/2	0/2	1/2	0/2	0/2	1/2	0/2	0/2	1/2
2*	2/2	1/2	2/2	2/2	3/2	1/2	0/2	0/2	0/2
8*	6/8	1/8	7/8	6/8	5/8	4/8	3/8	0/8	1/8

* Includes one patient presenting with two neuromuscular syndromes.

** Expressed as number of cases with finding per total number of cases in group.

TABLE VIII
*Concurrent Illnesses, Neuromuscular Syndromes and Muscle Biopsy Findings***

	Cases	Atrophy, random	Atrophy, patterned	Sarco-plasmic degeneration	Necrosis	Inflammation	Incr. connective tissue & fat	Abn. inter-muscular nerves & MEP	Arteritis	Normal
HISTORY STEROIDS (Total = 16)										
<i>Neuromuscular Syndrome</i>										
Myositis	4	4/4	1/4	3/4	3/4	3/4	2/4	1/4	0/4	0/4
Other myopathy	1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1
Other myelopathy	1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Neuropathy	9	7/9	3/9	5/9	5/9	4/9	1/9	3/9	2/9	1/9
Other dis. affect. muscle	1	1/1	0/1	1/1	1/1	1/1	0/1	1/1	0/1	0/1
ARTHRITIS (Total = 18)										
<i>Neuromuscular Syndrome</i>										
Myositis	5	4/5	3/5	4/5	4/5	3/5	2/5	3/5	0/5	1/5
Other myopathy	6	5/6	1/6	4/6	3/6	2/6	2/6	1/6	0/6	1/6
Neuropathy	4	4/4	1/4	4/4	3/4	3/4	0/4	2/4	1/4	0/4
None	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	3/3
SCLERODERMA (Total = 7)										
<i>Neuromuscular Syndrome</i>										
Myositis	2*	2/2	1/2	0/2	0/2	0/2	1/2	2/2	0/2	0/2
Other myopathy	2	2/2	0/2	2/2	2/2	2/2	1/2	0/2	0/2	0/2
Neuropathy	2*	2/2	2/2	1/2	0/2	0/2	0/2	1/2	0/2	0/2
None	2	0/2	0/2	0/2	0/2	1/2	0/2	0/2	1/2	1/2
LUPUS ERYTHEMATOSUS (Total = 3)										
<i>Neuromuscular Syndrome</i>										
None	3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	1/3
POLYARTERITIS (Total = 6)										
<i>Neuromuscular Syndrome</i>										
Other myopathy	1	1/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1	0/1
Neuropathy	5	3/5	2/5	4/5	4/5	4/5	3/5	1/5	5/5	0/5

* Includes one patient presenting with two neuromuscular syndromes.

** Expressed as number of cases with finding per total number of cases in group.

TABLE IX
*Concurrent Cerebral Disease, Neuromuscular Syndromes and Muscle Biopsy Findings***

	Cases	Atrophy, random	Atrophy, patterned	Sarcoplasmic degeneration	Necrosis	Inflammation	Incr. connective tissue & fat	Abn. inter-muscular nerves & MEP	Arteritis	Normal
ENCEPHALOPATHIES* (Total = 36)										
<i>Neuromuscular Syndrome</i>										
Dystrophy	1	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Myositis	1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1	0/1
Other myopathy	5	4/5	3/5	2/5	1/5	1/5	1/5	0/5	0/5	0/5
Myasthenia	1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Weakness secondary to encephalopathy (e.g. hemiparesis, bulbar syndrome)	12	4/12	3/12	4/12	2/12	1/12	1/12	1/12	0/12	2/12
None	16	1/16	1/16	1/16	1/16	1/16	1/16	0/16	1/16	12/16

* Includes patients with seizure disorders, organic mental syndromes, visual field defects and weakness secondary to cerebral disease.

** Expressed as number of cases with finding per total number of cases in group.

TABLE X
Correlation of Common Clinical Signs with Selected Biopsy Abnormalities

Clinical sign	Cases	Inflammation	Segmental atrophy	Sarcoplasmic degeneration
Muscle tenderness	29	13 (45%)	8 (28%)	14 (48%)
Muscle atrophy	106	34 (32%)	58 (55%)	64 (60%)
Fasciculations	46	5 (11%)	35 (76%)	20 (43%)
Pathological reflexes	45	7 (16%)	24 (53%)	15 (33%)
Peripheral sensory changes	86	25 (29%)	37 (43%)	44 (51%)
Incidence of abnormality in total patient population	348	101 (29%)	115 (33%)	170 (49%)

LEGENDS FOR FIGURES

FIG. 1. Patient "M", age 13, on whom the first muscle biopsy was performed by Griesinger and Billroth in 1864. Biopsy was taken from left deltoid muscle (note incisional depression). Copied from Griesinger (1).

FIG. 2. Camera lucida drawing of biopsy from "M" prepared by Billroth and Frey, showing replacement of muscle by fat and connective tissue. copied from Griesinger (1).

FIG. 3. Longitudinal paraffin section of normal muscle biopsy, fixed under light tension. Most structural elements of the fiber can be visualized by light microscopy. Z-lines (arrows) demarcate the sarcomeres (Trichrome, $\times 2280$).

FIG. 4. Electronmicroscopic section of normal muscle biopsy. Z-lines of the sarcomere are designated by arrows ($\times 26,400$).

FIG. 5. Histochemical sections are used to study various structural elements. Mitochondrial adenosine triphosphatase activity shows the orderly arrangement of mitochondria ($\times 1068$).

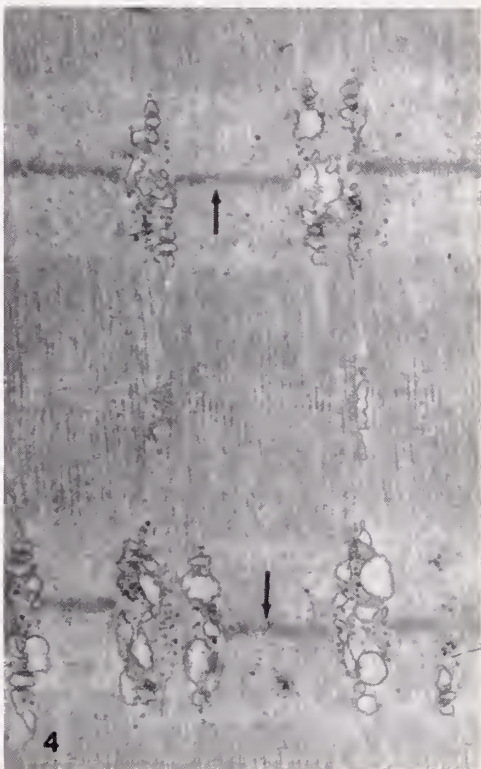
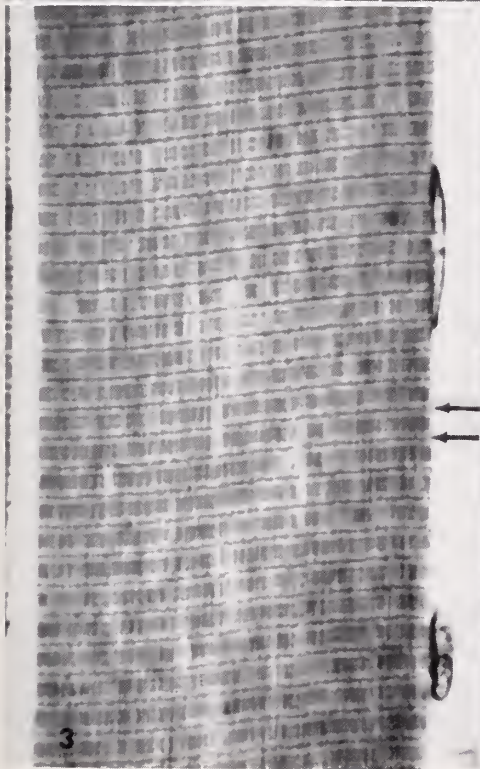
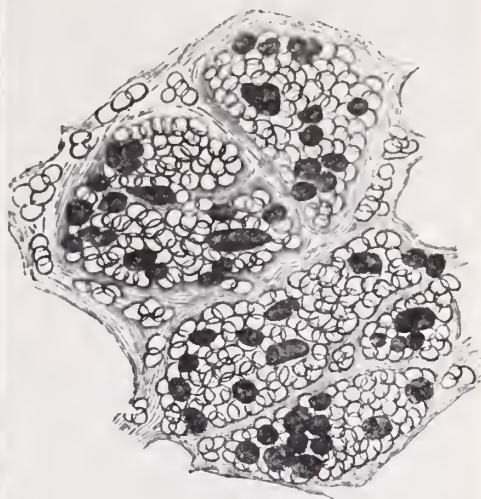
FIG. 6. Non-mitochondrial adenosine triphosphatase activity is associated with the sarcoplasmic reticulum ($\times 1068$).

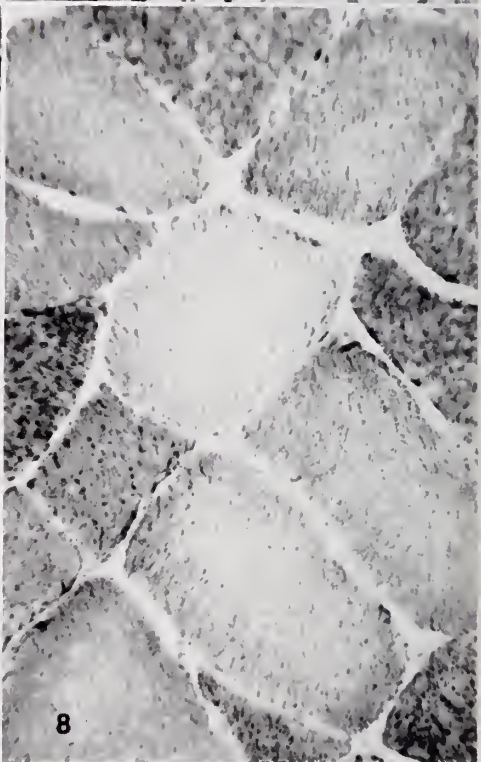
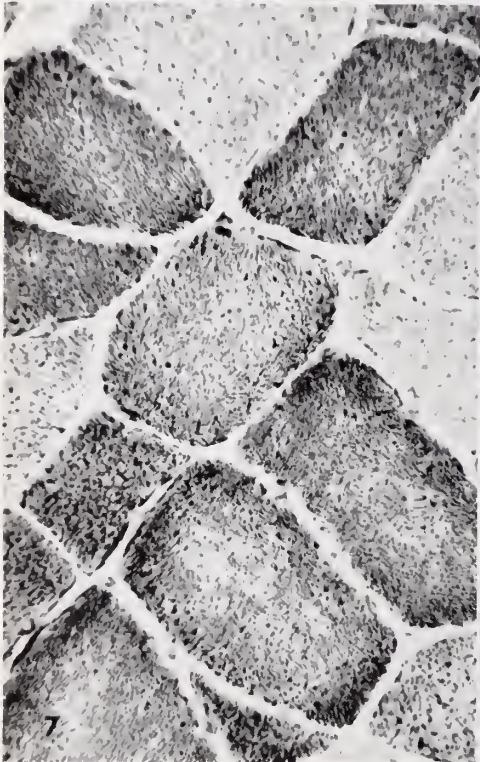
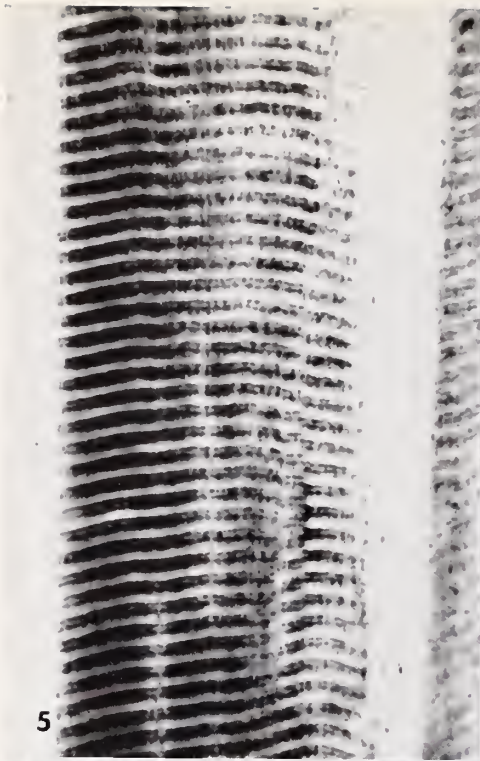
FIG. 7. Oxidative mitochondrial enzyme activity associated with type I fibers is visualized as dark formazan reaction product in mitochondria (Succinic dehydrogenase, $\times 382$).

FIG. 8. A serial section, adjacent to that in Fig 7, when incubated for type II oxidative reactions shows more intense activity in type II fibers and less intense activity in type I fibers. Menadione-linked alpha-glycerophosphate dehydrogenase ($\times 382$).

FIG. 9. Combined esterase-Bielschowsky silver preparation showing terminal axon dividing as it contacts motor end-plate. The latter is slightly out of the plane of focus ($\times 1231$).

FIG. 10. Cross-section of normal muscle fiber. Orthogonal diameters are used for measurement. The major axis (A) connects the two most distant angular points. The minor axis (B) is the longest perpendicular offset from the major axis which connects with any remaining angular point (H & E, $\times 881$).





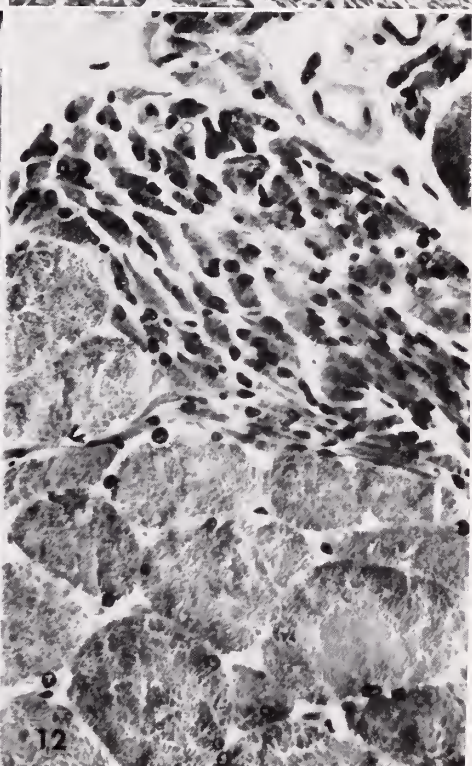
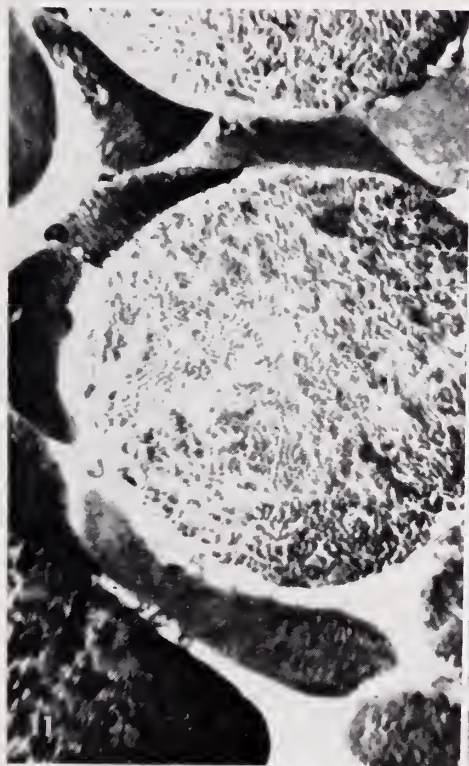
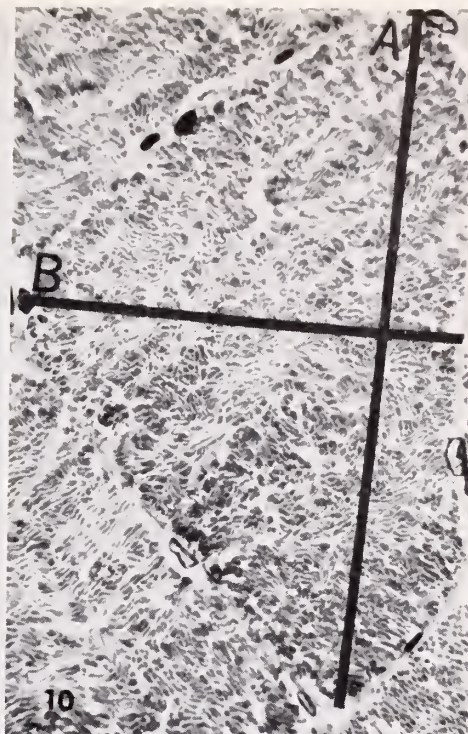


FIG. 11. Segmental atrophy involving small groups of fibers (H & E, $\times 854$).

FIG. 12. Segmental atrophy involving large groups of fibers (H & E, $\times 254$). $\times 254$).

FIG. 13. Atrophied fiber showing angulation (H & E, $\times 513$).

FIG. 14. Loss of the normal polyhedral contour results in rounded fibers (H & E, $\times 1121$).

FIG. 15. Aberrant fibrils may curve or coil around the longitudinal axis to form a ring fiber (Trichrome, $\times 988$).

FIG. 16. In some diseases ring fibers may be associated with peripheral sarcoplasmic masses (Trichrome, $\times 935$).

FIG. 17. Fibers with floccular change show irregular aggregates of dark-staining sarcoplasm (*arrows*) (H & E, $\times 564$).

FIG. 18. Optically-empty vesicles of varying size are observed in vacuolar change (Trichrome, $\times 801$).

FIG. 19. The target fiber (so designated by W. K. Engel) contains a central dense zone surrounded by a more or less concentric clear zone. In cross-section the fiber resembles a target (Trichrome, $\times 908$).

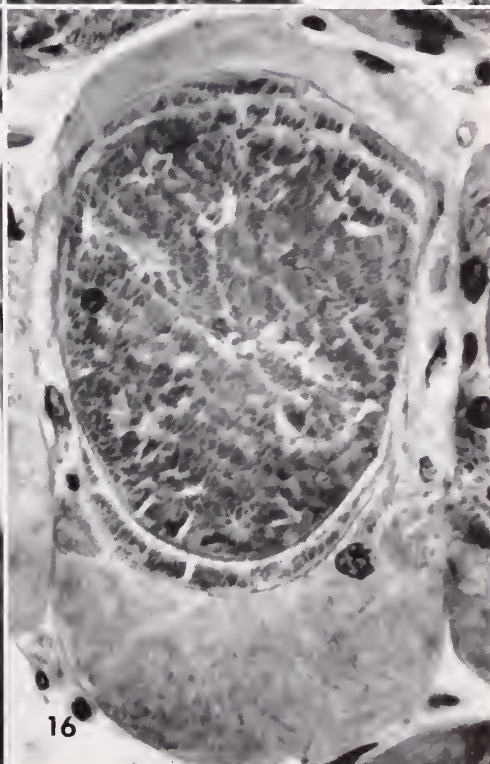
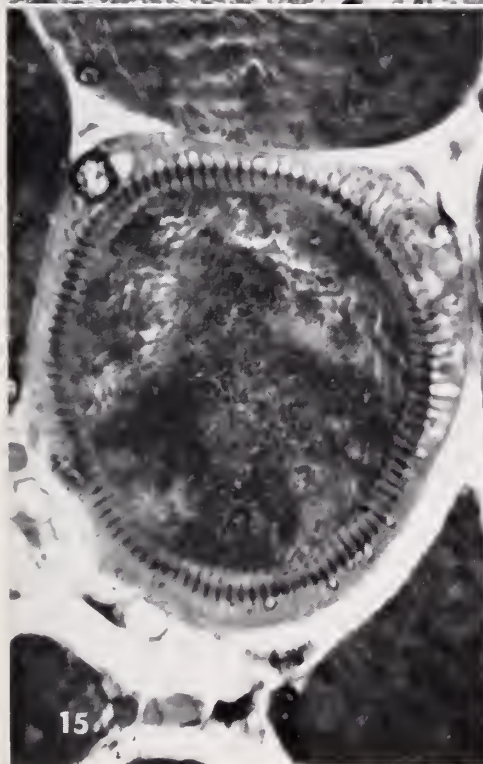
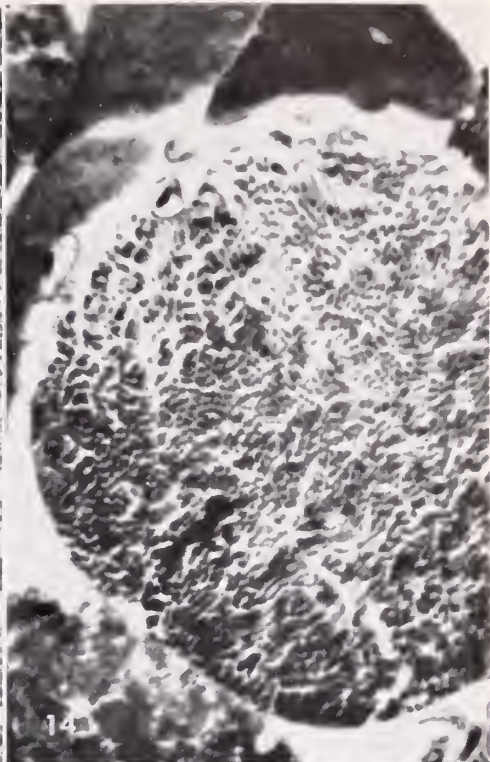
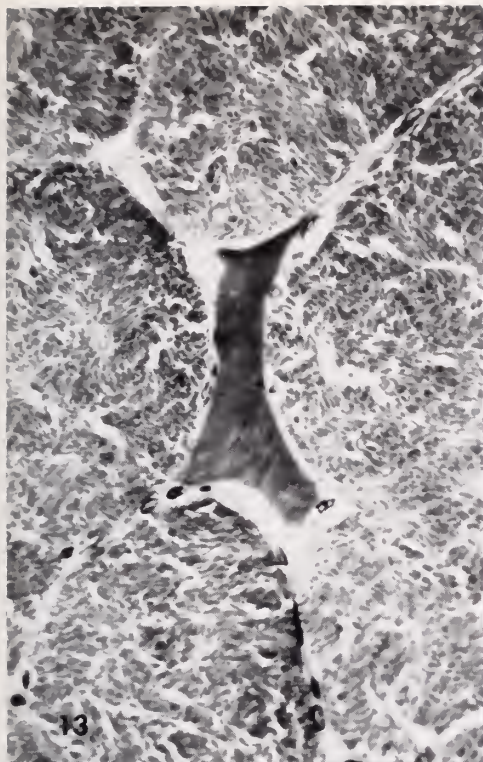
FIG. 20. Sarcoplasmic changes may ultimately lead to frank necrosis with invasion by macrophages (H & E, $\times 935$).

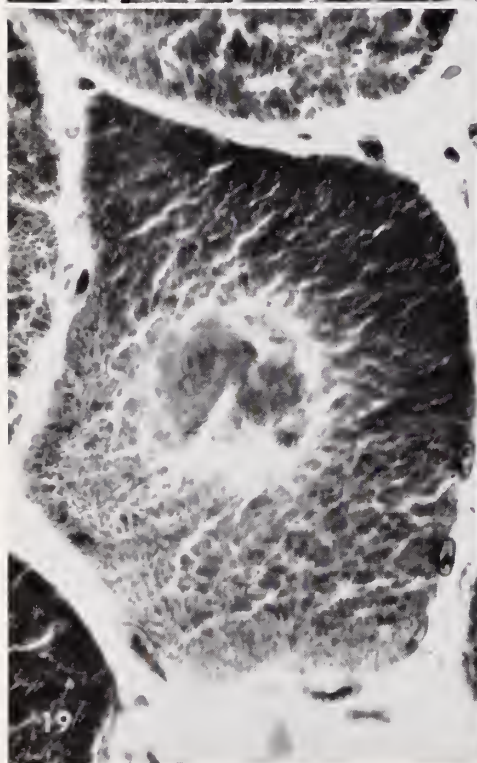
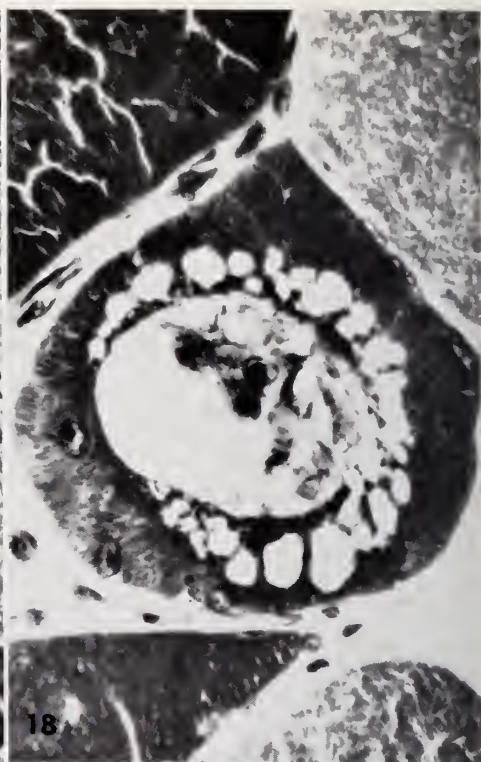
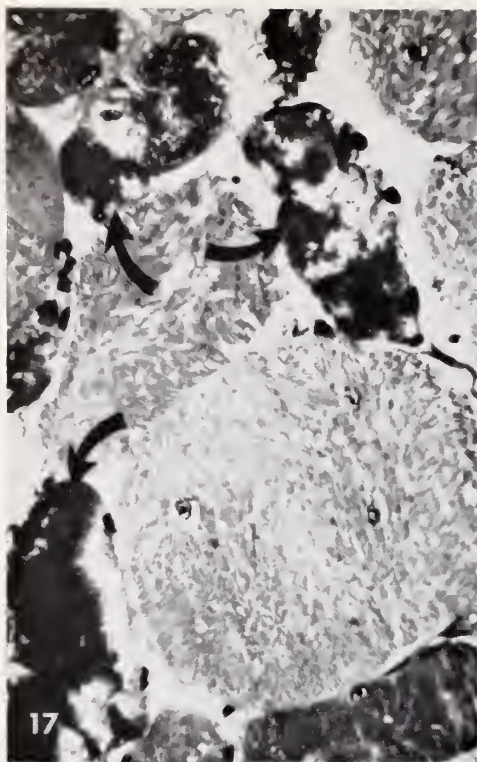
FIG. 21. Fiber splitting consists of longitudinal division of fibers. This is usually accompanied by septae of connective tissue and in cross-section the fiber appears to be divided into segments (*arrows*) (Trichrome, $\times 935$).

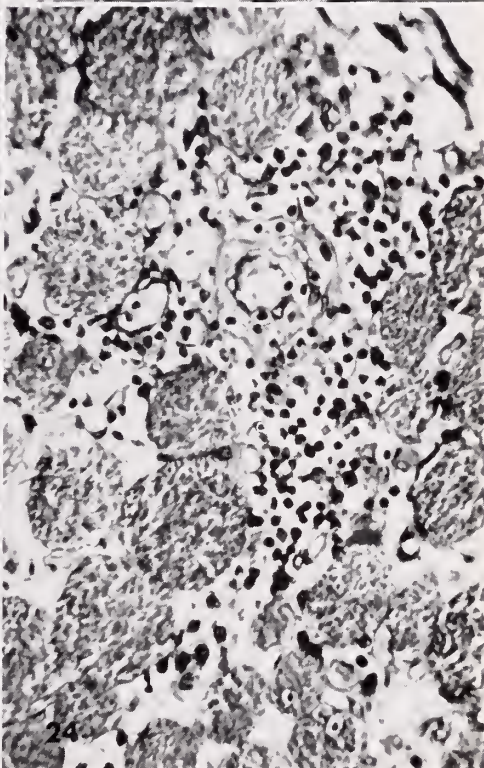
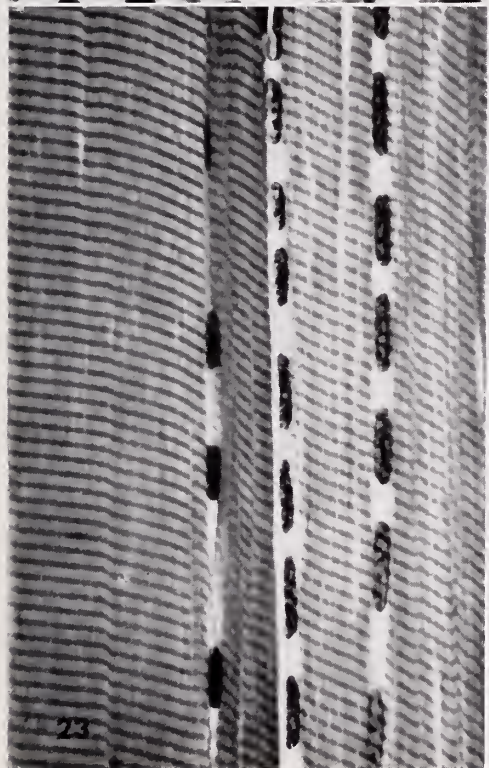
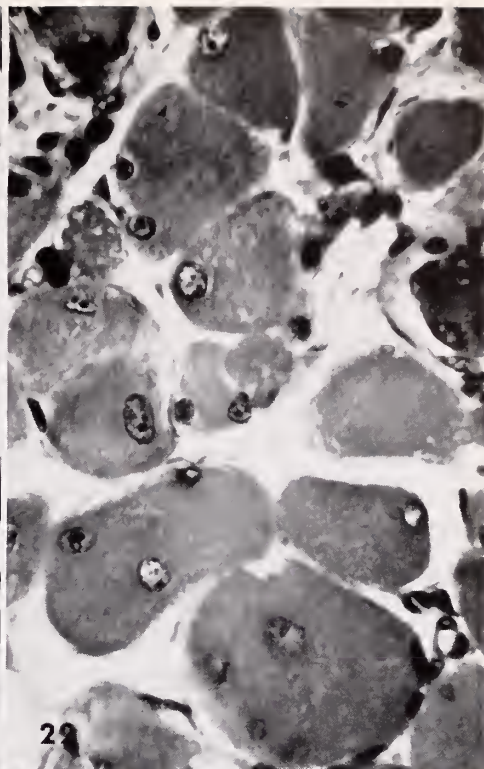
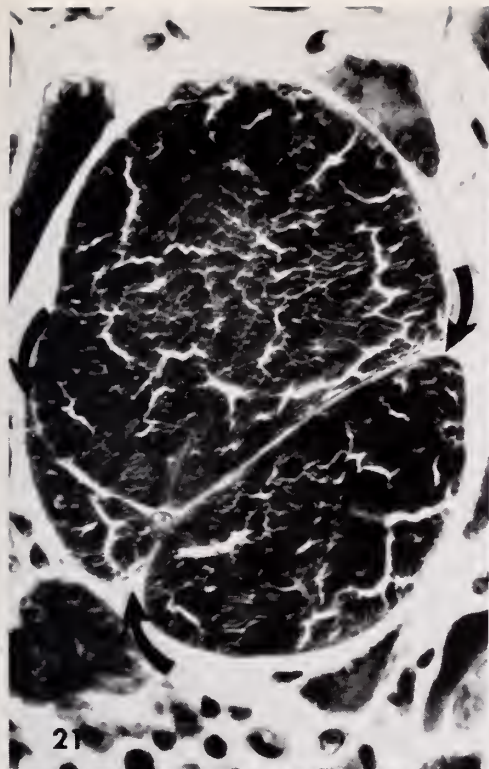
FIG. 22. Internalized sarcolemmal nuclei often exhibit a vesicular appearance (H & E, $\times 684$).

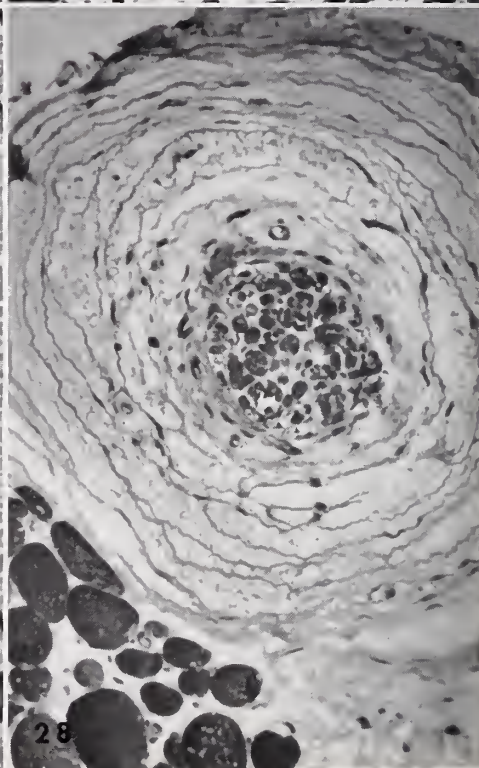
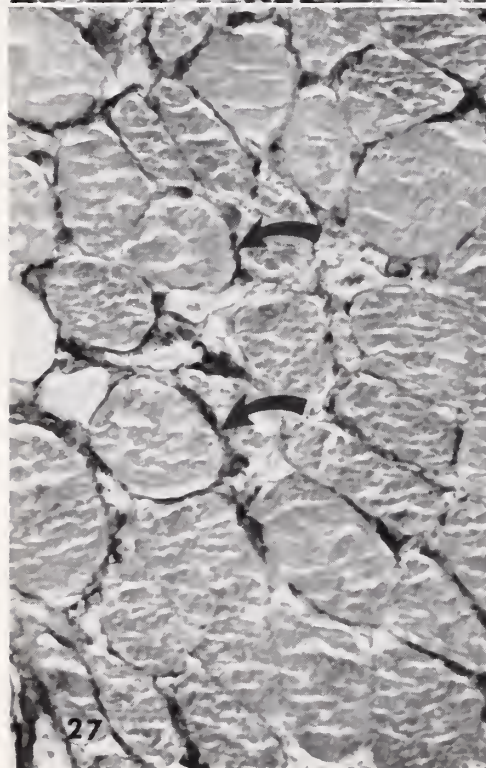
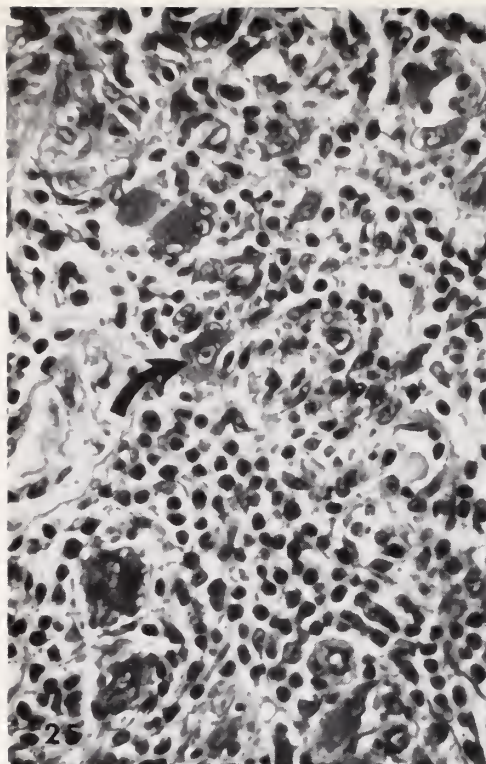
FIG. 23. Nuclear chain formation consists of linear arrangement of closely approximated nuclei on the surface or interior of the fiber (H & E, $\times 616$).

FIG. 24. Focal inflammation consists of more or less well circumscribed aggregates of inflammatory cells, often confined to perivascular areas (H & E, $\times 240$).









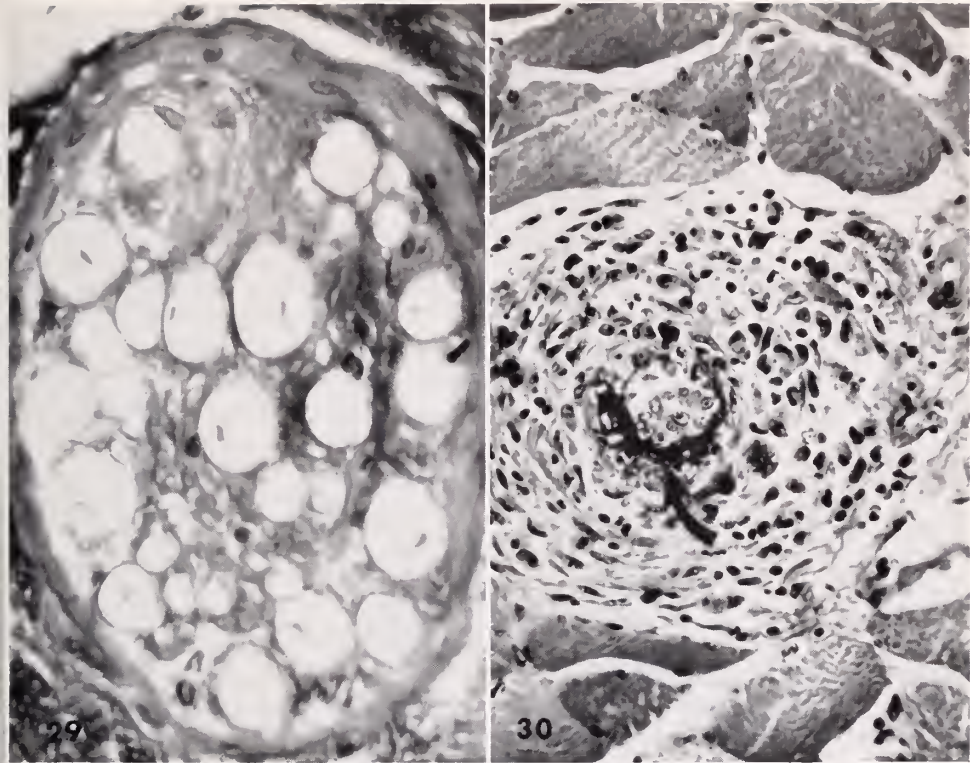


FIG. 25. In diffuse inflammation, surviving fibers (*arrow*) are separated by large numbers of inflammatory cells (H & E, $\times 428$).

FIG. 26. Trichinosis. The search for possible causative organisms in inflammatory reactions may involve the study of large numbers of serial sections (Trichrome, $\times 530$).

FIG. 27. Increased endomysial connective tissue (*arrows*) (Trichrome, $\times 545$).

FIG. 28. Capsular thickening in a muscle spindle (Trichrome, $\times 255$).

FIG. 29. Intermuscular nerve with marked reduction of nerve fibers and pronounced increase in endoneurium (Trichrome, $\times 941$).

FIG. 30. Polyarteritis with inflammatory infiltration of vessel wall and fibrinoid necrosis (H & E, $\times 436$).

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Indications: Meprobamate is effective in relief of anxiety and tension states. Also as adjunctive therapy when anxiety may be a causative or otherwise disturbing factor. Although not a hypnotic, meprobamate fosters normal sleep through both its anti-anxiety and muscle-relaxant properties.

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Precautions: Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of pre-existing symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses. Mild reactions are characterized by an urticarial or erythematous, maculopapular rash. Acute nonthrombocytopenic purpura with peripheral edema and fever, transient leukopenia, and a single case of fatal bullous dermatitis after administration of meprobamate and prednisolone have been reported. More severe and very rare cases of hypersensitivity may produce fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic in such cases, and the drug should not be reinstituted. Isolated cases of agranulocytosis, thrombocytopenic purpura, and a single fatal instance of aplastic anemia have been reported, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity has been reported, usually after excessive meprobamate dosage. Suicidal attempts may produce lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

Usual adult dosage: One or two 400 mg. tablets three times daily. Doses above 2400 mg. daily are not recommended.

Supplied: 'Miltown' (meprobamate) is available in two strengths: 400 mg. scored tablets and 200 mg. coated tablets. 'Mepro-tabs' (meprobamate) is available as 400 mg. white, coated, unmarked tablets.

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TRENDS IN NEW MEDICAL SCHOOLS

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Foreword

The collection of essays presented herein is concerned with ideas and problems engendered by the development of a new medical school. The primary thought was to dedicate one issue of the *Journal of the Mount Sinai Hospital* to the Mount Sinai School of Medicine. It became apparent, however, that many of the problems of this school had general applicability, not only for other neophyte schools, but for established institutions desirous of reorganizing their educational structure. Therefore, we decided to present a discussion of the problems of a new medical school to a wider audience. The thoughtful and stimulating contributions obtained from leading medical educators from various parts of the world were assembled in this book, in order to assist those who grapple both with the problems of new medical schools and the more general field of medical education.

The scope of new medical schools includes a great variety of related and unrelated areas, from the specifics of individual medical disciplines, the goals of medical teaching, the relation of the medical school to the university and the community, and to architectural problems. It is impossible to offer a reference book comprehensively reviewing all questions involved. This collection, therefore, remains a series of articles written by persons dedicated to medical teaching, with a particular interest in the development of new medical schools. No attempt was made to enforce uniformity of style or organization, or to avoid repetition. Some of the essays are referenced and others are not. Thus, the editor's job was quite easy, since he depended mainly on the good will of his friends to put their thoughts on paper. He also exploited the good nature of his wife, who translated the foreign papers, and of his co-worker, Dr. David Koffler, who helped conscientiously in the organization of this volume. The *Journal* and The Mount Sinai School of Medicine want to thank all the participants for their congenial cooperation. The Editor is particularly grateful, even if he does not always agree with the frequently divergent thoughts of individual contributors. He hopes, however, that the content will be as stimulating and rewarding for the reader as it was for the Editor.

Hans Popper

MEDICAL SCHOOL—COMMUNITY RELATIONS

Medical Education: Medical Technique or Disease Control?

George James, M.D., M.P.H.

It may be safely assumed that many contributors to this volume will deal at length with the scope and content of the future medical curriculum. The present writer's career has been spent largely in the realm of local governmental health services, an unusual background among those now dedicated to medical education. He will therefore limit his present contribution to a consideration of certain aspects which, though they are now becoming increasingly pertinent, have so far been rather consistently neglected.

The Role of the Medical School

The ultimate purpose of a medical school is the promotion of health. While some patients may be treated directly, as in an affiliated teaching hospital, a medical school's major pressure for health is indirect, expressed through its graduates.

There is a built-in lag between most things a medical school does and their practical result. What is taught the medical student in his first year is not used by him as an independent practitioner for a half-dozen years at least, and often not until much later. Even what is taught in the last year of medical school may not be applied in practice for four or five years. The graduate physician is always dealing with a situation that has changed from that which existed when he attended medical school.

Medical schools, therefore, have to be especially alert to trends in health problems so as to make a reasonable projection of what those problems will be six or a dozen or two dozen years in the future. This is not only a question of estimating the nature and extent of emphysema years ahead as it is of developing a fair picture or profile of the overall situation in which the doctors of the future will be working. It is relevant to know the likely extent of a problem such as emphysema; it may be even more relevant to project the extent of further urbanization in the nation, the expansion of the old age population, and changes in dietary habits.

Ineffectiveness of Present Measures

It is comforting to look backward and reflect on the accomplishments of medicine, especially during the century of the germ theory, but it is more useful to consider the future and how we are to attain it with optimal success.

Dean, Professor and Chairman, Department of Community Medicine, Mount Sinai School of Medicine, New York, New York.

If we really examine medicine today, the conclusion is inevitable that in terms of impact on our major health problems we do not have excellent medicine, we have poor medicine (1). Among the 20 leading causes of death, today's medicine is making a major change in the trend of only a few. We do rather little which is highly effective for coronary heart disease, much less than we would like about cancer, and hardly anything to prevent stroke. We know a good deal about how to achieve first rate rehabilitation, but we actually bring it to only a small fraction of those who need it. Home care programs, desperately needed for the health maintenance of older persons, are in their infancy.

Deficiencies in Medical Care

Much of American medicine, as given in our best teaching hospitals, is superlative in quality, especially in the field of acute illness, no longer our major problem. But 90 per cent of all medical care in this nation takes place somewhere other than at the hospital bed, and relatively little of it in teaching hospitals. As we move down from that pinnacle through proprietary hospitals and nursing homes, quality declines and many patients receive inadequate care. Often small things keep people from care: the creaky oldster who cannot cross the street in the time it takes the light to change is a case in point. So is the low-income father who does not get to a clinic that closes at 4:30 PM because he is afraid (frequently with good reason) that he will lose his job if he leaves work before 5 PM.

In this and similar cases, it is the packaging of medical care that repels the patient. Unless the receipt of medical care is made practical for the sick individual, he will wind up rejecting it. When this happens, his chronic illness can lead to what we recognize as a preventable disability. The public treasury then pays for terminal care, often at a cost far greater than earlier preventive measures would have entailed. The needless humanitarian loss cannot be calculated. There are no metric units in which to measure the personal misery that can result when, because of the lack of disease detection programs, a woman suffers terminal cancer of the cervix instead of having it detected sufficiently early to be cured.

The present splintering of medical care is such that it is not uncommon for an individual with several chronic complaints to spend nearly full-time getting to and from clinics and waiting in them. The result is unnecessary unemployment and family breakdown—or the patient abandons altogether the search for adequate care.

Quality in Medicine

The provision of equal access to medical care for any substantial part of the population as under Medicare leads to two possibilities. The first would reduce everyone to a lowest common denominator. We would spread our present faulty system even thinner than it is. Everyone would be guaranteed a fair share of inadequate care. This would be like assuring equal access to going where one does not want to go.

The second more difficult road requires that pressures for quality be built into equal access programs. Improvement in quality is achieved through research and demonstration, through new knowledge, new drugs, new methods of prevention, new techniques for delivering care. The NIH programs have resulted in a huge force to drive upward the quality of medical care.

It is now necessary to make it rewarding for health personnel and institutions to give high quality care, and unrewarding for them to give low quality care. In New York City, for example, the municipal government will pay for the hospital care of medically indigent patients only if certain examination procedures (such as chest x-rays) are routinely performed. A hospital may decline to adopt these procedures, but then it will not receive municipal money. In practice the hospitals acquiesce and procedures thus established for one group of patients are usually extended to others. It is hoped that Medicare programs will adopt similar pressures to improve quality now that their virtual monopoly of payment for indigent medical care renders impotent such local efforts as noted above.

In reorganizing our medical system, we must encourage dissatisfaction and promote experimentation. We need extensive demonstrations to show how new patterns of medical care can be useful. Typical of such demonstrations are the Queensbridge Health Maintenance Service for the Elderly (2) and the New York Hospital-Cornell Medical Center Project (3). Additional information on ways in which medical organization can improve has come from experience at New York University with evening and daytime arthritis clinics (4) and from cancer detection efforts at the New York City Health Department (5).

The Physician's Role

It is commonly assumed that health matters are the doctor's business, but in practice he shares them. Laymen, from members of Congress to the boards of voluntary hospitals, make important medical decisions. A committee of laymen, in a state capitol or in Washington may make decisions that determine whether an elderly patient with two chronic illnesses has to travel several miles between two clinics or can receive comprehensive care in one building.

The picture of what the practice of medicine consists of has become fuzzy and so has the image of who ought to practice it. For example, chest surgery is medicine and should be taught in medical schools. But chest surgeons in a good teaching hospital can save about one out of 20 patients with cancer of the lung. If our seventh grade school teachers could motivate their students not to smoke cigarettes, they could save probably ten or twelve times as many. Would they then be practicing medicine? Is the practice of medicine purely the replication of a technique, or is it the purposeful employment of measures which actually can control disease most effectively? In a similar vein it may be noted that the engineers who add fluoride chemicals to the water supply of New York City are able to do more for the control of dental caries than can all 8,000 of our local dentists working beyond what they are now doing. Again, is it relevant to concern ourselves solely with definitions of the practice of dentistry?

Many people will participate in giving medical care and in research and demonstration. Some will not be doctors, although skilled in the performance of certain techniques. But if doctors do not provide the leadership, do not provide those effective combinations of basic research, clinical practice and outside resources needed to achieve success, then movement toward better quality, will be slowed or stopped. Granted that our major need is the improvement of quality, then the essentiality of medical leadership must become obvious.

We have already seen welfare departments seeking to control medical programs seemingly unconcerned about building in pressures which will insure a steady improvement in comprehensiveness and quality.

The national Heart Cancer and Stroke program is on sounder ground. This is an area plan based at the centers of quality medicine (the medical school and affiliated teaching hospital). The pressure in this plan is toward spreading that quality out into the community instead of keeping it fenced in. Projects are reviewed and approved by a jury of peers. Grants are made for a couple of years, and then new applications for other grants must be made. The program is structured for upward movement with accent on high quality spread to the total group of communities in the large area of the region.

The Nature of Our Health Problems

There is much for doctors to do in building together the separated parts of our medical care system. But the doctor of the future will also be led outside the boundaries of traditional medicine by the nature of our major health problems.

Many of the great killers of the past could be attributed to one micro-organism or another. The causative factors in today's major killers and cripples form a much more complicated picture, especially since they increasingly include important manmade pressures toward illness. Human behavior is strongly implicated in our first four leading causes of death: heart disease, cancer, stroke and accidents. These conditions (if accidents may be called a condition) are responsible for nearly three times as many deaths as all other conditions put together.

Most of these conditions are not only killers, but major causes of disability. The most important "condition" causing widespread disability that rarely causes death is the group of ailments listed in the National Health Survey as "arthritis or rheumatism." Rheumatoid arthritis is certainly of unknown cause. Much osteoarthritis, despite interesting relationships to wear and tear and prolonged mechanical imbalance, undoubtedly is also. Factors tending to bring on these conditions are less clearly identified than in coronary disease, but it does appear that there may be less total disability from them if people could be motivated to take reasonable and regular exercise throughout their lives, and to avoid obesity. At least no other suggestion has been made which appears as useful.

For some specific situations within leading causes of death and disability

we have highly sophisticated treatment techniques. Open heart surgery, for those who need it, can be a dramatic miracle. In arthritic conditions surgery can sometimes work wonders, as it may in some few patients with early cancer of the lung. No one would deny the usefulness of penicillin in subacute bacterial endocarditis, nor the marvels of electronic pacemakers. There is a need to improve and expand such techniques and through research, to add to them. Undoubtedly technical breakthroughs will occur which will help make it possible for us eventually to change the trend of our major causes of death and disability.

But as of the foreseeable future, to make an impact on these major problems will mean going beyond traditionally medical techniques. To do something massive about lung cancer we will have to use our best surgery, and we will also be involved in questions related to the economics of the cigarette industry, to the packaging and labeling of cigarettes, to advertising, to the training of children, and to the establishment of disease detection programs.

In coronary heart disease, if we are really to deal with the problem in a relevant way, we will again find ourselves involved in cigarette smoking and in questions of diet concerning the food industry. We find ourselves involved with legislation and with advertising. We need our purely medical techniques, but to achieve disease control we will have to go far beyond them and train our new physicians to accept leadership in dealing with them.

Technique or Disease Control

The question has never been whether medical schools will teach the latest in medical techniques, as well as how to perform the research from which new techniques may be created. They will have to do that and do it imaginatively. As medicine becomes more complex there will be a growing need for effective specialized techniques and for those who can create, understand and use them. At the same time, we are suffering today from techniques that exist but are under-used, that do not reach many of the patients who need them.

The object in medical education is to prepare the doctor for the situation into which he is going. Thus we have to teach him his new role beyond traditional medicine without detracting from his opportunity to learn the knowledge and techniques he will need. Our job is to make doctors broader and more community-involved at a time when specialization tends to narrow them, and when there is growing concern among layman and professional that the average doctor tends to be an ignoramus or worse regarding almost anything outside of medicine (6).

There is ample evidence that breadth can be taught in medical school. Students at the University of Kansas Medical School who participated in an experimental home care program developed quite different attitudes than those who did not participate (7):

The home care students were significantly more psychologically oriented than organi-

cally oriented. They cited primarily patient-centered rather than disease-centered objectives of patient care and were concerned with social rather than biological factors to a significantly higher degree than students in a control group. In addition, the frequency with which hostile or derogatory statements were made about a hypothetical patient was significantly higher in the control group.

To deal effectively with today's and tomorrow's problems, medicine must learn how to organize around the patient and his family, must concern itself with his social needs and his relationship to society. Medical problems in the next 20 years will to a large extent be fought by dealing with economics and politics and fighting the deficiencies of society itself. Nor is this wholly new: who can say how much of the advance against tuberculosis came from the use of medical techniques and how much from a rise in the standard of living? He who tries, must admit that the data clearly indicate that medical art and science have exerted the weaker influence.

Medical men should be in charge of medical matters. Yet there is more and more likelihood of control of medical programs by people without medical training. This is the doctor's own fault. He has allowed himself to organize as opposer rather than as builder. As new medical programs have developed, non-doctors have rushed in to fill the vacuum left by the physician's abandonment of the areas beyond the fringe of traditional medicine—areas which are crucial to the control of disease today. If we do not teach the specialist at least enough about society to understand what it is of which he is a part, then the quality of medicine will further suffer. He runs the risk of being demoted to the status of a technician, skilled perhaps, but still relegated to a minor role increasingly to be defined by others.

In moving toward the teaching of community medicine to the doctor, we are really deciding whether medical men can be given this broader background no matter what their ultimate specialty. Fortunately, they will not all be alike. Some will be drawn more toward one area or another. It is hoped that all will learn something of this new medicine and that there will at least be enough of those accepting full leadership so that physicians can eventually have their full say and influence in the working and negotiating with the non-medical parts of our society that will be necessary in reorganizing our medical care system. Our medical schools must accept this task of training these medical leaders to whom must be entrusted the solution of the medical problems of tomorrow.

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The Medical School—Community Expectations

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There are few countries in the world today which do not find themselves coping with the tide of rising expectations in the field of health services on the part of its citizens. In the less well-developed, less industrialized and poorer portions of the world, where the mass of the people themselves are not fully aware of the benefits to be gained from the availability of modern health services, political forces are at work which are aware of these opportunities.

The value of preventive, diagnostic and curative health services as well as public health measures, is being increasingly understood everywhere today, not only at top leadership levels but also among the citizenry. While this interest is less evident in the underdeveloped areas, the plans for social, political, economic and industrial development which are being produced by national and international bodies, political and/or expert, all are giving increasing attention to the protection and the improvement of the health of all the people as an essential element of progress and development.

The interest of the public in health and in health services is emerging as a force in the development of nations, regions and states. This interest is based upon the recognition that health is a vital national concern, not only because of the relation of health to productivity, but also because of our new notions about human rights and human dignity. All Western countries recognize that medical care should be available to all, regardless of their ability to pay, bringing the best service to them when they need it. Planning for development in the rest of the world, despite the difficulty that faces these countries, is proceeding on a much more overt basis and includes attention to the provision of modern health services.

The protection and restoration of the health of human beings rests upon a number of fundamental points. These include the standard of living generally, nutrition, pure water supply and safe sewage disposal. These public works measures are, however, not a substitute for the preventive, curative and rehabilitative personal health measures which depend upon physicians, nurses and associated professional and technical personnel using appropriate facilities and organizational patterns.

Thus, medical schools are crucial to the further development of health services. George Berry has said:

The medical schools are the well-springs whence will flow the better health of tomorrow. They must constantly adjust their educational offerings for future doctors to the changing conditions and needs of society.... Good medicine cannot be prac-

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ticed independently of the intricate framework in which other health personnel function. The clinical medicine of the future will be indissolubly a part of the future organization of medical service, with all relevant professional activities, facilities and finances (1).

The role of the medical school as the keystone to the development and improvement of health services is accepted. More and more attention is being given, notably by governments at all levels, to the growth of existing medical schools and the establishment of new ones, to meet the pressing need for health service personnel.

Medical education is not a monolithic process which moves forward on all fronts in precisely planned fashion. The expectations held by various professional, academic and citizen forces committed to the support of medical education are as diverse as the background surrogates of reference and appraisal of these sections of the community. Many objectives or elements in medical education and in the health services system of the community interact with each other. The day-to-day, as well as the long-term, balance of the wide range of activities in the medical school determines the extent to which the medical school fulfills its goals—as seen by a variety of university, medical and community groups.

Many medical educators believe that “whatever is good for medical education is good for patient care and the health services of the community we serve.” Such a broad statement, though true in a long-term general sense, is of limited use because it disregards the natural tendency of the researcher or educator to be impressed with the vital role of his field of expertise. Thus, it is difficult to see who will speak for the patients and the community when issues of patient care and community service arise. The needs of individual patients may arouse the deep interest of the faculty clinician and stimulate him to effective action. This, however, is not synonymous with a balanced planned program of care based upon the needs of patients and the community *as such*.

In the United States medical education has been highly organized and of generally high quality for several decades. New medical schools are being developed in many parts of the country. Increased governmental financing is available for these educational programs. This financial support which started primarily for research activities was followed by support for education in special fields, for research facilities, and now for educational facilities.

At the root of this support by the public is the identification of the public with the objectives of medical schools in terms of its own welfare. The public wants results now—not only long term. It not only wants cures for disease over the long term (and it is learning to have the patience to await the long range results of basic research), but it also wants more and better doctors. It wants the more rapid application of what is already known on behalf of the entire population. It wants accessibility to physicians and medical services and effective interest in its health problems—on the part of doctors and related personnel.

Medical education is usually said to be dependent on teaching, research, and patient care. Though these interact, the problems of emphasis and balance raise difficult questions for which precise answers are not always readily discernible.

How much research should a medical school undertake? How much teaching is appropriate for a faculty member? How much patient care should he undertake? What is the appropriate balance needed so that this tripod will not be tipsy? (2) In recent years the character and priority of functions of the medical school and of its affiliated institutions have been the subject of much discussion. Medical educators, foundations, governmental agencies and legislators have begun to wonder whether the overwhelming emphasis on research productivity characteristic of United States medical schools since World War II is not hindering the achievement of the medical schools' major responsibility—the education of the medical student. If faculty promotion depends primarily, as generally appears, upon research productivity, the younger faculty member is tempted to guard jealously his time for research and to allow this activity to predominate over his educational and patient care responsibilities. At the same time, it is important to recognize that the teaching load of the faculty must not be so great as to jeopardize creative research. Another danger is the assumption of a load of patient care, which is so large in relation to staff and facilities that the standard of performance suffers, thus resulting in an unsatisfactory framework for the education of the student.

What type of patient care best serves the objectives and needs of medical education? What types of cases provide the greatest learning opportunities for the student; illustrations of health problems which the practicing doctor will frequently encounter or those which satisfy the specialized research interests of the faculty?

This author recently studied the viewpoints of many medical schools in the United States regarding the achievement of balance among the goals of education, research and patient care. The report written with his colleagues (3) states:

There is no doubt that the goals of education, research, and patient care provide a common ground upon which medical schools and hospitals can unite in close association. It is the problem of finding the satisfactory balance that creates uneasiness and frustration. . . . The suggestion is therefore made that a fourth goal be added to provide greater understanding and stability: the goal of community service. This is viewed as being different from, and larger than, patient care. Patient care, in terms of medical care for the individual is, of course, a form of community service. Research and education are also forms of community service.

The study group conceives of the goal of community service in a somewhat different context than patient care, the latter being aimed at the individual in the relatively narrow sense. By community service is meant a willingness on the part of the teaching hospital (and the faculty of the affiliated medical school) to take its proper place in the whole range of health services needed in the community. It is intended to mean what has often been termed 'readiness to serve.' This may mean staffing a well-organized emergency ward and an adequate service for walk-ins who need medical care even though it is not of emergency nature. It may mean providing a psychiatric service, a service for alcoholics, or

for patients with infectious disease. It may mean operating a unit for long-term care, affiliating with a nursing home, taking part in a home-care program or many other possibilities.

Although it is understandable, and often times even desirable for the individual professor to be single-minded and dedicated to his research and training, it is the study group's opinion that it is most regrettable, if not unforgivable, for hospitals affiliated with medical schools to be less than fully aware of their broad responsibilities toward the goal of community service. Where a teaching hospital is actively making efforts to pursue the goal of community service, it follows that the medical school with which it is affiliated must be ready to share these efforts wholeheartedly....

Obviously, in the larger cities, neither a medical school or its affiliated hospitals can, by themselves, possibly provide all medical care to the entire population. Nor can they try to do so without jeopardizing their goals of excellence in education and research. There is no community, however, in which the medical school and its affiliated hospitals cannot act as leaders in planning and organizing health services for all. They can and should, in the opinion of the study group, so relate themselves to the community's health services as to enrich its resources and assist in making sure that every person in the community receives the amount and kind of high-quality medical care that he needs. The medical schools and their teaching hospitals have an orientation toward excellence in medical care; the special skills of their faculty and staff members can be extremely valuable in organizing community health services. If they reject responsibility to demonstrate the best in medical care and to assist in community organization for health, then these vital developments, if they are initiated at all, will have to be undertaken by other individuals who have far less appropriate preparation and experience than a medical school faculty and teaching hospital staff. Surely, the precious resources in scientific and technical personnel that are found in highest concentration in medical schools and teaching hospitals must make the maximum contribution possible for the health interests of the community....

They should be expected to enter into community research projects and demonstrations of new and more efficient methods of solving the principal health problems of their community e.g. chronic illness and disability. Most of these problems require local community organization for solution, and the medical school and its affiliated teaching hospitals form a natural and desirable focal point for such organizations. Community service, in the sense described here may never be, and perhaps never should be, a primary goal for a medical school. It is nevertheless one which, from the observations of the study group, a medical school can and should share with its affiliated hospitals and its community. Only in this way can the medical education it offers and the research it pursues assume active leadership in the organization of health in the United States today.

These are the reasons for setting forth the goal of community service as a distinct entity representing a major element in the community's expectations.

It is helpful to think of this matter in terms of ends and means. What is an *end* for the medical school is a means, in terms of emphasis, for the hospital and the community and vice versa. For the general hospital and the community, the brilliance and effectiveness of the educational and research activities of the medical school hardly compensate for serious deficiencies in patient care, should they exist. The concept of the four goals, each related to the others, is helpful in understanding the problems and potentialities in the activities and responsibilities of the medical school, especially in terms of diverse expectations by different forces in the community.

Leaders in medical education in the United States have recognized the need to reassess the role of the medical school as an institution with long term so-

cial purposes. In April, 1965, a planning committee of the Association of American Medical Colleges submitted a report (4). The opening paragraph of the transmittal letter by the Chairman of the committee states:

The great and growing national concern over the health of our people requires that those responsible for medical education, today and in the future, turn their attention to a question of the greatest importance and the most far-reaching consequences: *Will the methods and practices currently followed in providing health personnel of all categories, together with the programs and facilities in being or planned, be adequate to meet our national needs?*

In addition to medical authorities, this committee consulted such community representatives as state governors, legislators, members of Congress, executives of United States government agencies, the executives of Blue Cross, and insurance companies.

In listing the seven outstanding implications for medical education of trends in health care the first is the "need to devote increasing attention to the requirements of the nation." The closing paragraph of this section states:

There is, perhaps, no implication of emerging trends that has more profound significance for the field of medical education today than the need to give increasing attention to the growing health requirements of the nation. Positive assumption of responsibility and positive action—and this alone—can keep the initiative in the hands of those best prepared to plan the destiny of medical education.

Another implication listed, of special interest in this context, is entitled "Need to improve delivery of health services." The key recommendation in this regard is:

Schools of Medicine should be taking the lead in studying the ways medical care is delivered to patients. Their concern should be not only with acute care but also with preventive care and rehabilitative care. Their concern should be with comprehensive family care as well as with specialty care. The university-sponsored medical school is in an unequalled position to draw upon the resources of many disciplines—medical practice, economics, business administration, sociology, psychology, education, engineering, and others—to study the way in which comprehensive health care is provided. The need is for careful study of how health care can best be made available—including how medicine can best be practiced—and for the development of more effective plans of organization and delivery of health care. . . . Findings should be reflected in instruction at all levels. Specifically, teaching future physicians and persons who will work together as teams in caring for patients should be approached in ways that will perfect effective team working relationships and establish them as desirable and appropriate.

The increasing appreciation of the shortage of scientific personnel throughout the world and the mounting cost of medical care underline the need to equate the delivery of quality care with methods of doing this with a minimum of waste. Medical faculties have a responsibility to demonstrate the best medical care in such a manner. If they abdicate responsibility and interest in evaluation and experimentation within the medical care setting, whence will come the standards of quality and effectiveness? Medical care research which is done imaginatively and scientifically can provide objective guidance for

modification and change. New ideas can be introduced most effectively when they are supported by relevant facts.

Though the responsibility for medical professional education rests with the relevant sciences in the universities, the responsibility for adopting objectives must be shared with the community through its representatives, notably government. The people of the United States have interest in supporting basic research. Medical schools will nevertheless be judged by the number and kinds of doctors and related health personnel which they develop. The community is content to have the research activities conducted by medical schools judged over the course of time. Support for medical education, however, either on a voluntary or on a tax basis is primarily aimed at fulfilling pressing medical care tasks effectively, scientifically and with due consideration to the dignity of the public. The expectations that the community has of medical schools cover a range of immediate and long-term hopes and aspirations. Both sets of expectations merit serious and continuous attention. The acquisition of new knowledge is of little value to the community if clear-cut plans and purposeful programs to apply such information to the restoration and protection of health are not consistently undertaken.

The four goals, education, research, patient care, and community service cannot be substituted one for the other. Though each of these helps the other, there is a problem of emphasis. The community expects effective performance towards each of these goals in the immediate and also the long-term sense. This provides new and creative opportunities for medical schools in fields which can yield gratifying harvest if they are tilled scientifically and purposefully.

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The Wedding of an Off-Campus Medical School with a Community of Moderate Size

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As the title of this paper suggests, a medical school joining a city with a population of around 200,000 cannot remain aloof but must become an integral and contributing part of the community if it is to achieve a state of harmony with its surroundings. In a very large city, comparative isolation is more plausible. A medical school built on the campus of a university in a rural setting will have to make only minor adjustments with the local medical profession, but where the school has been sought by an urban area as an economic asset and where the medical profession regards it as both a threat and a prize, the school must give thoughtful consideration as to exactly how it adapts itself to the community.

In June of 1965 the Trustees of the University of Massachusetts voted by a slim margin to build their medical school in Worcester—60 miles from the main campus and 40 miles, in the other direction, from Boston. After some controversy, this decision was subsequently upheld, and plans are being made to implement it. As in the building of all medical schools, certain problems are entailed by the site and other factors which are peculiar to that school. The ones pertaining to our school will be presented with solutions partial or complete which seem reasonable under our circumstances but might not be for another institution. These problems are related to the off-campus location and to our relations with the community.

The reasons for placing a medical school on the campus of its parent university have been recounted so many times that there is no need to repeat them here. The difficulties of building the school elsewhere are not often delineated, and yet must be faced and overcome. One of these, perhaps not immediately apparent, is the lack of sponsorship by an institution of considerable local power and prestige which a university provides when it builds a medical school on its own grounds. In a distant and sensitive community, the school's decisions stand as its own without any umbrella of protection from its sponsoring institution. This means that any steps that can lead to general or particular criticism must be taken carefully after approval by the Trustees and with support in the press and by leading citizens.

More particular problems arise from the distance between the university and the school. The normal activities of the top men in the basic sciences include research and the education of candidates for the master's and doctor's degrees in their specialties. We can provide space for research, although the help of physicists, geneticists, mathematicians available on the campus will be

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lacking unless we hire our own, but we cannot provide the easy relations with the graduate school so vital to the education of basic scientists which is readily attainable when that school is situated on the campus. This poses a problem in recruitment of the preclinical faculty. Furthermore, our program of education for nurses, technicians and others who must have their liberal arts education in the college of arts and sciences are rendered much more complicated by the separation of the schools. This also will affect any plans for integrated education with the undergraduate college. In the administrative field we must maintain our own business offices, mechanical and other services independent of and often duplicating those already existing on the campus in Amherst.

There are, however, advantages to this separation. The first is the avoidance of the friction which occurs when a highly paid, somewhat technical, medical faculty exists in close proximity with their more academic, less well-supported colleagues in the rest of the university. The second is that some of a medical school's policies, particularly those related to the appointment and functions of the clinical faculty in the hospitals, are not at all in conformity with accepted policy in the rest of the university. Our variations from what is required at Amherst may be overlooked or condoned if we are far from the parent institution.

In facing the difficulties posed by the distance from the main university, we have come up with both immediate and long-range plans for overcoming them. The most pressing problem is that of recruitment of preclinical faculty in the face of expanding departments in older schools and the demands by new schools more advantageously located than our own. Some support for research programs can be solicited from the faculties of existing colleges in Worcester which have modest offerings in the graduate fields. Some may be available from the Worcester Foundation for Experimental Biology which has an excellent staff and is interested in cooperating with us. For the rest we must turn to our main university or those in Boston for the help we need. Arrangements have been made tentatively with the graduate school in Amherst for the development of cooperative programs leading to the master's and doctor's degree in the basic sciences. Commuting is out of the question as the time involved would be too great (3 hours a day), but students could live and work on the main campus for one or two semesters in succession and then move to ours for a similar period. This will require careful scheduling of courses, research work and teaching time on each campus as well as extra housing in Worcester, but it can be done. Similarly we are approaching nursing education with our nursing school in Amherst and the training of technicians, social workers and others so that we can correlate their hospital experience with their liberal arts courses in an effective manner. In projecting our teaching programs over the years we can only regard these as stop-gap measures which are less than ideal. What we really need is an intimate association with a full-fledged university possessing an excellent graduate school. In contemplating this prospect after deciding to place the school in Worcester, it was

apparent that we should get enough land next to the school so that, when the time was ripe, a branch of the university could be built of which the Medical School would be a part. Massachusetts, richly endowed with excellent private colleges and universities, has lagged behind the rest of the nation in public support of higher education. The expansion and development of the university are recent, but it is growing rapidly and already has a small branch in Boston. Applications for admission are, however, outstripping facilities so that hopefully another branch might be created by the Legislature next to the medical school within the next 20 or so years. To provide ample land for this possibility, we abandoned the other sites previously considered for the school and moved to a location where we have already obtained 124 acres and can, by purchase or exchange with other governmental agencies, obtain a total of at least 350 acres, which would be enough for the eventual establishment of a complete university. The history of the medical school at the University of Alabama emphasizes the wisdom of this planning. It was built in a city remote from the main campus, and is now having to acquire land through urban renewal to expand into an entire university.

Our relations with the city of Worcester, its doctors, hospitals, and other institutions pose problems similar to those being faced by a variety of schools although varying somewhat in their intensity. The initial reception of the school by public officials, private individuals, doctors, and hospitals has been excellent. Maintaining this atmosphere will depend in essence upon close attention to our public relations. We have found that there is very little understanding by the public of what a medical school is or how it conducts its various programs of education and patient care. This means that advantage must be taken of every opportunity for speaking before different groups or with individuals so that the knowledge of how we will operate can be fully comprehended. The technique of perpetuating good-will relies heavily on there being some person representing the school who can answer questions or discuss problems with city officials or any other group. This turns the school from an inaccessible governmental agency into a responsive instrument, sensitive to public and private feelings. In this context we have given great consideration to all applicants for jobs and those referring them even when the possibility of applicants for jobs and those referring them even when the possibility of employment has been remote. The purchase of land, whether from private individuals, other State agencies or such organizations as churches can easily provoke unfavorable publicity, regardless of how pressing the need is for the school, if not handled properly. We have fared well so far in this regard by going to the City Manager and other public officials as well as to the officers of the Chamber of Commerce for assistance. This, however, is not enough. Personal contact with the individuals concerned, availability for conversations or meetings and visiting them in their own homes has been vitally necessary.

Hospitals and doctors have delicate relations with any new school, but these vary to some extent from one locality to another. In general, our dealing with them has been guided by two principles. The first is that a new medical school is created to turn out practicing physicians and to provide continuing

education. It should, therefore, support the medical profession and be sure that its programs interfere as little as possible with established patterns of teaching and patient care. Second, that any hospital invited to climb into the school's connubial bed should do so as an equal partner and not as a subordinate. Worcester already has a State mental hospital, two community, one church, one proprietary, and a municipal hospital. Four of these have training programs; three do some teaching of medical students, mostly on an affiliated basis. The quality of medical care is high in the city; a number of the doctors have had teaching experience and desire to extend this. Undoubtedly a number of physicians, however, established their practice in that locality because they were interested only in patient care and had no desire to teach.

Our hospital consultant urged us, as did deans of other schools, not to take over and rebuild an existing hospital as the home-base for our full-time faculty, but to construct our own university hospital attached to the medical school. Realizing that such a hospital, if it took on a community function, could seriously hurt the patient care and training and programs of the existing hospitals, we decided to establish it as a referral hospital only. We will, therefore, construct a small hospital (400 beds) not sufficient in itself to handle 100 students in a class, but not apt, either, to remain largely unoccupied for a long time. Additional units of 400 beds to be added later are being planned. Hence, we will soon need affiliations with some of the services at different hospitals in Worcester where there is already an interest in and experience with teaching, and where the student will profit from intimate contact with able practicing physicians. We have believed that these affiliations would work best if the heads of our departments chose the services with which they wanted to affiliate in conjunction with their chiefs rather than if an administrative decision was made for affiliations with an entire hospital, prior to the appointment of faculty. The details of the relationships between these services and the schools have been determined and are generally acceptable to the hospitals and the doctors. We will take onto our faculty the members of the affiliated service who wish to teach with rank appropriate to their qualifications, including the head of the service. Those who do not want to teach will retain their present status undisturbed. Future appointments to the service will be made jointly by the hospital and school; presumably, a requirement for this will be the ability and desire to teach. When the head of the service retires, an ad hoc committee of men from the hospital and the school will define the purpose and program for the service for the future, decide what sort of a chief it should have, find and select him. Their recommendations will then be submitted to the hospital and the school in the routine manner for approval or disapproval. It is our feeling that this gradual conversion of a hospital service from essentially a community function to one including a considerable responsibility for teaching is more conducive to the peace and tranquility in which teaching programs thrive best than would be complete transformation of a service at the outset by appointment of medical school faculty to run it.

We believe that one of our cardinal responsibilities in the community will be the support of its institutions, medical and non-medical, to the extent of

our ability. In this regard we think that the design of our buildings, situated as they will be in a conspicuous location on a main artery, should by means of their architectural design, make a major contribution to the appearance of the city. Working arrangements or some form of mutually beneficial relations should be developed between the colleges, research institutions and various paramedical community organizations and our medical center when pertinent. These might include use of our facilities for meetings or for offices, or combined programs of teaching, research and so forth. We have already reached a basic agreement with the small but distinguished Worcester Medical Library for a partnership in a combined library at our school. The joint use of a computer with other institutions is being explored. Pleasant working relations with a number of community services have been initiated.

The atmosphere in which a medical school functions is extremely important to its well-being. A medium-sized community, to which a school and its hospital are a major addition, reacts noticeably to every action of the school. Harmony can best be achieved by close personal attention to relations with others and by giving continuing consideration as to how the school can contribute by its programs and facilities to the well-being of the community. Although separation of a medical school from the main university is undesirable, many of the handicaps entailed can be overcome. Hopefully, this problem will eventually be solved by the addition of other schools and departments to the medical center until a complete university is formed.

Community and Professional Problems with a New Medical School

Merlin K. DuVal, Jr., M.D.

There are many facets to starting a new medical school. Taken together they may present a picture which is quite unlike that which is presented when a new graduate college is started in another field. Taken individually, each facet may reflect a strikingly different picture depending upon the position of the observer. In this chapter consideration will be given to one facet which ordinarily receives very little emphasis for the good reason that it lacks the glamour and excitement which are intrinsic to the academic, curricular and fiscal problems of starting a new school. This facet is the impact which the arrival of a new medical school has on the community in which it is located.

Generally, the arrival of a new graduate college does not require very much in terms of advance community preparation since the college can be accommodated without strain by those who live and work in its vicinity. Therefore, it is only natural to ask, "Why is medicine different?" The explanation is simple: medicine, in order to be taught, must be practiced. It is this practice requirement, or clinical medicine, that creates an interface between the medical school and its surrounding community. This interface can be most conveniently analyzed under three headings: city, hospital and professional. In any given instance, each of these factors may be represented to a different degree depending upon the size of the city in which the medical school is to be developed, whether the school is to be tax-supported or privately endowed, and whether or not there is already a medical school elsewhere in the same vicinity. However, while their degree of representation may vary, all are invariably present.

Consider some of the "city" factors first. The physical plant for a college of medicine presents a very substantial building. It requires power, utilities and the disposal of a wide variety of wastes some of which may be radioactive, contaminated, etc. Its location will affect zoning, automobile and truck traffic and the residential and commercial interests of near-by neighbors. Its presence may unbalance existing city transit systems and increase police and security problems. In other words, once it has been constructed, it is probably going to cost the city some money while, at the same time, the land on which it is located is removed from the property tax rolls. It has been suggested that this is rather like a de-annexation program in which community services to the de-annexed area may actually have to be increased.

On the other hand, the arrival of the medical college can be readily

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recognized by community leaders to be a substantial asset. It is a "blue chip" investment that pays off in dividends much beyond anything that can be estimated in advance. The design and construction of the physical plant itself will provide many jobs, some of which are perpetuated by the constant remodeling, renovation and growth which are characteristic of such institutions. The annual operating budget of the plant will approach one-third the value of the initial capital cost of the building and approximately 75% of this annual budget is for labor. A superb market is created for supplies, equipment and utilities, and medical center visitors require gasoline, food and overnight lodging. In other words, in strictly the commercial sense, a new medical college represents a product that is eminently salable to the community in which it is to be located. However, it will not sell itself. Those responsible for its inception must educate and inform the community leaders of these benefits. Not until we have done so can we expect appropriate assistance when the time comes to request help with rezoning, property purchase, the widening of some roads and vacating of others. The members of our city councils, our planning and zoning commissions and our Chambers of Commerce understand these matters and are invariably eager to be helpful if consulted early.

The hospital factors are of a different character. Hospital operation is rarely a profitable enterprise. The sudden intrusion of a college of medicine, which owns and operates a teaching hospital or will control certain community beds, necessarily requires the very earnest and deep concern of persons who are involved in the operation of hospitals in the vicinity. The principal reason for this is that the arrival of the college of medicine will usually generate a requirement for additional hospital beds. Whether or not the additional beds are university-owned or are made available through the existing hospitals in the community does not affect the requirement that they are needed. This inevitably prompts the fear that the opening of new beds, for teaching purposes, will result in a drop in the occupancy rates of local hospitals and thus a loss in operating efficiency. (Paradoxically, this is not what really happens. Instead, the arrival of a college of medicine seems to result in the attraction of a substantial volume of new patient material into the community. The result is that occupancy rates do not fall; instead, the number of patient days of service rises.) The problem which is produced by the arrival of the new beds relates to the increased patient services which must be provided from a pool of paramedical personnel which is usually of relatively fixed size. The net result is that the talents of these employees must be spread more broadly. This thins the ranks, increases the wage scale and adds to costs. The heightened competition for employee services which takes place during this period of adjustment may have peripheral ramifications of consequence such as erratic turnover, wage inequities and feelings of enmity.

There is very substantial evidence which indicates that the seemingly difficult "hospital" factors of the interface between a new medical school and its community are more than compensated by features of a positive nature. In fact, there is no evidence that a community hospital has actually

closed because of the opening of a new medical school except and unless such closures were prearranged between the involved parties. Instead, hospitals have apparently gained as a result of the proximity of the medical school. It is the prospect of such gains which should be emphasized in the advance planning for a new medical school. For example, the community beds may be used for teaching purposes; internship and residency programs in community hospitals can be strengthened, perhaps even inaugurated if they do not already exist; teaching conferences can frequently be improved; sophisticated equipment may be made available and shared; additional income will be generated; inpatient hospital research may begin; records will improve; accreditation will be easier, etc. There are too many possible benefits to list them all in one article. Even more important is the influence which the arrival of the college of medicine invariably has on the establishment of new programs of paramedical education for health personnel such as nurses, laboratory and x-ray technicians, physical therapists and dieticians. Since it is these persons who constitute the working force of the community hospital their production in increased numbers is the absolute answer to the provision of bedside service for the greater number of patients which will be attracted to the community. In this regard, intelligent planning for the utilization and deployment of existing community health personnel and facilities is more necessary now than ever before. We have probably been much too slow in recognizing that hospital planning is a community venture, indeed an obligation of some magnitude. The era of the small, proprietary hospital is rapidly disappearing and we are fast becoming dependent upon a sustained and effective level of community support for our larger health facilities. This support is emphatically easier to achieve if the community has planned for it. The relatively recent establishment of hospital planning councils in metropolitan areas is beginning to accomplish these purposes. Participation by community medical leaders at these council tables has added a new dimension to the lay understanding of the problems related to the distribution of medical care.

One of the most difficult of the factors is that which relates to the interface which is created between the medical school and the practicing members of the medical community. It was stated earlier that medicine differed from other graduate colleges in that it had to be practiced in order to be taught. This creates a situation in which the medical school, in effect, competes with its own alumni by drawing on many of the same resources on which their practices are dependent. Worse, the two parties are often bound by different rules. The problems which can arise from this circumstance are so great that, three years ago, the Association of American Medical Colleges devoted its entire Tenth Teaching Institute to the subject "Medical education and Practice." The deliberations which took place at that meeting were thorough indeed; yet, they fell short of providing the necessary answers to the problem for the good and sufficient reason that there probably are no answers. However, it is possible to avert a substantial conflict by conceding that physicians in the vicinity of the new school have a right to feel apprehensive about its

arrival. This apprehension has many sides and colorations; and although its expression may vary from individual to individual, it takes its origin from a single, common base. This base is the awe in which the physician holds such an institution. It is unreasonable to expect a practicing physician to feel completely comfortable and compatible when he is alongside an institution which he holds in such awe because of the contradiction and fear its presence incites. Basically, he knows that it is to his advantage to be near his professional school if possible. He is proud of it, draws satisfaction from identifying with it and would like to be a part of it himself. His apprehension develops when he realizes that he might be left out as it develops. Paradoxically, he may develop an additional fear that, if included, he will somehow fail to measure up and carry his own weight. The result of both is the same; namely, a threat to the standing he feels he has achieved among his colleagues.

The practicing physician is also concerned that those at the college of medicine will be interested in him as a person and will invite him to make a contribution to the growth and development of the educational and research programs of the school. Those whose orientation has been primarily inside the academic sphere are often surprised, albeit unwarranted, that so many sound ideas about medical education can arise from thoughtful members of the profession who are outside the school. These ideas may range from research projects to nominations for faculty positions, program emphasis to curriculum innovations. It matters less what the ideas are than that they be expressed. Every effort should be made to construct appropriate administrative machinery for the receipt of these ideas and viewpoints since more important even than the ideas which may be advanced is the opportunity which their transmission offers to the academic administrator for extra-academic communication. This need pose no threat whatsoever to the principle that policy and decision-making with respect to the school will continue to rest with the university. This is not ordinarily challenged by practicing physicians.

There are a few specific areas of concern about which feelings will run quite high as the new medical school develops. These problem areas, if given the consideration they deserve, invariably tax the resources and patience of both the academic and the practicing groups. For example, those questions which relate to the production of income by salaried members of the clinical faculty are going to be of considerable interest in the community. Although it can be readily proven that a salaried member of a clinical faculty cannot possibly do any substantial economic damage to the professional community, as long as his efforts are expended within the limits of a few basic ground rules, the specter of unequal competition in a game in which both sides may not be bound by the same rules is a formidable one indeed. Experience has shown that this is an area in which advanced preparation is worth every ounce of energy and every hour of time that can be invested in it. Generally, members of the practicing profession who are close to a new medical school are surprisingly generous when they discuss potential solutions to some of these problems. However, this generosity is most apt to be present in response to an early consultation with

them. If they have participated in the deliberations which lead to final decisions on such points as the production of income by salaried members of the faculty, they almost invariably become staunch defenders of the programs which follow. Of course it is a mistake to attempt to seek a complete unanimity of opinion. There will always be a few persons to whom the threat of a good school of medicine is so utterly overpowering as to cost them their objectivity.

One observation has been proven to be extremely interesting. When the town and gown factions seem to be in disagreement over a specific point it can be shown that they are usually not in disagreement at all. Instead, the two groups have simply arrived at different interpretations and conclusions from the same data. When this is the case, the bias which is inherent in either position may set the stage for a most uncomfortable situation when, instead, an increase in the frequency of intercommunication will obviate it. There is no greater danger to the relationship between two interested groups than that which is created, or persists, after one of them reaches a conclusion based on insufficient data or insufficient communication. Trust and confidence can only arise on a base of honesty and integrity earned through mutual efforts to understand the other view.

Quality medical education is a highly complex commodity to distribute. With the enormous increase in the investment in medical education and research which society is currently endorsing, the complexity of the distribution of this commodity will increase further. As a result, the medical center is rapidly achieving a type of influence which obligates it to guard carefully its relationships with the community around it if it is to succeed in its mission. The anticipation and preparation for these relationships in advance of the arrival of a new college of medicine greatly enhances the possibility of success in such a venture and is emphatically worth the time and effort required.

MEDICAL SCHOOL—UNIVERSITY RELATIONS

The University in Medical Education

DeWitt Stetten, Jr., M.D., Ph.D.

The prime subject matter taught at the earliest of the European universities, that at Salerno, established in the ninth century, was medicine. During the ensuing Middle Ages, other professional disciplines, notably law and theology, appeared as proper subjects in university curricula. It is interesting and important that historically the university is grounded in its professional schools, that the early purposes of the schools at Salerno, Bologna or Paris were to produce physicians, lawyers or clerics. Scholarship *qua* scholarship appears to have been predominantly a monastic function and only secondarily, as scholars were attracted to or developed on university campuses, did scholarship become a prominent university goal.* The medical educator may hold his head high in the academic community. His school is not one of the adnexa of the university. Rather is it the gamete from which the entire structure grew. Although often regarded in the American university tradition as the prodigal stepchild of the university, the medical school is in reality its progenitor.

The history of the typical American university is quite different from that of universities in general. Often it is an outgrowth of an earlier college of arts and sciences to which, by process of merger and accretion, a variety of other schools have been added. These may include schools of law, engineering, theology, agriculture, education, business administration, public policy and graduate (Ph.D.-oriented) schools of arts and sciences. They may also include schools in the health-related fields of medicine, nursing, dentistry, public health, veterinary medicine, pharmacy, etc. To fund, construct, staff and administer such a vast complex as a major American university is an extraordinarily complex and difficult job.

The only real benefits that the participating schools derive from membership in a great university are the opportunities to interact with other schools in other disciplines, or more specifically for the members of the several faculties and their students to mingle with and exchange ideas and information with their counterparts in other fields. If such interplay happens abundantly and profitably, then the time and talent invested in pulling and holding together a university may have been well spent. Alternatively, if each school of a university

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* It will be interesting to observe whether, in conformity with a kind of phylogenetic law, the new Mt. Sinai Medical School, presently not affiliated with any preexisting university, will ultimately develop a complete 20th century university of its own.

pursues its own narrow path toward its own degree, its own profession, its own private goal, the whole concept of university becomes one of questionable merit.

It has been held for many years that it is desirable that a medical school be administered by and be part of a university, indeed, if possible, that it be situated on a university campus. Flexner iterated and Coggeshall reiterated these views. The present writer concurs enthusiastically with this attitude but subject to the proviso that something constructive and useful be made of the shared administration and the geographical proximity. Left to its own devices, it appears that each academic discipline, increasingly engrossed in its own affairs, pays progressively less attention to the affairs of its neighbors. Some planning and a conscious effort may be needed to effect useful contacts between faculties of medicine and of engineering, between students of law and of library science. To preserve complete academic and intellectual isolation even when surrounded by academia is unfortunately possible and seems on occasion to be the path of least resistance.

In thermodynamics we recognize an energy barrier which must be overcome if reactants, transiently in a metastable situation, are to react and so to proceed rapidly toward equilibrium. There is an analogous energy barrier separating the several departments of a school, the several schools of a university, from one another. We know that catalysts, including enzymes, may strikingly lower the energy barriers encountered in thermodynamics, reduce the so-called activation energies, thereby permitting enormous acceleration of chemical events. What, if any, catalysts can be exhibited to minimize the academic barriers on a university campus? If no such catalysts are available, what is the reason and need for a university?

Before pursuing these questions further, let us briefly consider the product which we are trying to create—the ideal physician. He is in some regards different from the other products of a university. We expect of him today a relatively high degree of sophistication in many sciences including chemistry, biology, physics, mathematics and the social sciences. He has been taught a profession, i.e., a way of life and a way of earning a livelihood through service to his patients and his community. We assume his continuing scholarship so that he may teach others and learn from his books and his own observations. Above all, he must have deep concern for humanity. While a medical student, he is at once a graduate student of sciences and of humanities, simultaneously acquiring professional skills. It is a tall order to be filled.

But it is far more complicated than that. Perhaps because of the intensity of the educational experience, perhaps because of the selection by the admissions processes at medical schools, and doubtless for other reasons as well, the physician produced may be a person of deep but narrow perspective. Law, government, economics and philosophy, in short, those areas of culture not closely associated hitherto with the practice of medicine, have been permitted to go by the board, and once this has happened, later reinvolverment with such matters is difficult and unlikely. Yet today and particularly tomorrow the well-rounded physician will be called upon to consider, develop and defend

opinions in areas where other disciplines impinge upon his. Sociologic and economic factors such as living standard, population density and urbanization obviously influence the nature of disease and its control. New bills are presented and passed into law which change the roles of the physician, the clinic, the insurance company and the patient. We have long dealt with private health and, to a limited degree, with community and so-called public health. Now we are confronted with a host of new problems in world health and already space health, represented by concern over such matters as the microbial population on the moon, has become a subject of interest to a limited number. Medicine, which formerly dealt with the intimate relations of patients and their doctors, has today become of great public concern. In short, medicine is in the news and a typical issue of the *New York Times* will contain four or more important medical stories. It devolves upon the medical schools to prepare physicians to function effectively in the environment.

In order to perform this minor miracle a medical school will do well to avail itself of all the assistance in the neighborhood. We are familiar with the uses that all medical schools make of the hospitals and physicians of the community to assist in teaching and training functions. For a university campus-based medical school, similar benefits to the teaching-learning process should derive from contacts with faculty and students of the non-medical portions of the university. Such contacts become the catalysts which diminish the energy barrier between the medical school and other units of the university.

How is such involvement of medical education to be accomplished? What are plausible goals to be set? Partial answers to both of these questions are already at hand in the practices of many university medical schools. Whereas there are many strong research ties and joint research programs between portions of a medical school and appropriate branches of the university, e.g., biomedical engineering, biomedical mathematics, medical applications of computer science, collaborations with members of chemistry, physics, biology, psychology and other departments, the impact of all this upon the teaching programs at the pre-M.D. level has been generally small. Medical jurisprudence is frequently offered in the M.D. curriculum, usually as a brief series of lectures covering such workaday matters as the rights and obligations of the physician on the witness stand and the proper behavior of the physician on observing a street accident. A summary course in medical history is often also available and will usually interest only those students whose knowledge of medical history already exceeds that material presented in the eight or so hours which the curriculum committee is willing to surrender for this frivolous purpose.

I should like to take the remaining space assigned to me to describe a small sample of programs which might be considered for testing and possible inclusion in medical curricula. Each of these programs would be elective and ungraded. The purpose, in each case, would be to widen the perspective of the participating student, to lead him into the paths of scholarship and citizenship beyond the levels usually expected of a physician, and to permit him to interact more freely with members of other professions.

Medicine and Law. Clearly the physician may in the future have much to do with Law beyond knowing the pertinent rules of evidence and the limits of his legal liabilities. He may wish to have an understanding and a sound basis for opinions on present and pending legislation. He should understand something of how lawyers think and what makes them tick. A lack of such understanding contributes to the hostility sometimes existing between members of these two professions.

A brief course of lectures is not likely to correct the basic difficulty. Far more effective might be an opportunity to argue issues of common concern. Students of medicine and of law, perhaps 5 or 10 of each, could be locked in a room, together with one bright member of each faculty. One or another topic involving an as yet unresolved issue could be raised for discussion. What are the rights and privileges of a patient scheduled to receive an investigational new drug? When is a physician entitled to perform a new procedure on a normal subject? What is the legal basis, what is the validity, of a courtroom diagnosis of insanity? These and many other questions could profitably be argued, not to establish legal verities but rather to provide opportunity for each profession to gain some insight into the mental processes, the morals and the prejudices of the other.

Medicine, Economics and Sociology. It will be the unusual physician of the future who can limit his activities to contacts with individual patients. The physician is already expected to become involved not only with the health and disease of the individual but also with the health and disease of the community. All of our towns, cities and states have their own chronic and acute maladies and the physician can scarcely disregard these. Examples are: urbanization, juvenile delinquency, increased availability of hallucinogens and other drugs, and each of these obviously has medical implications.

These and other unsolved problems of society may, in another generation, supplant infectious agents as major etiologic factors in human disease. It would be well to consider how these problems can best be presented to the medical students. Whereas a brief course of lectures by interested sociologists might help, it would be consonant with the general philosophy of medical education to place the student in contact with the problem. It is suggested that for the interested student a brief exposure to a slum area, with all its attendant problems, could be exceptionally rewarding. The student could be temporarily assigned to the school health office in an underprivileged area, there to study specific medical consequences of this particular environment.

The hospital is of course a community of particular interest to the physician and its many phases of operation are probably adequately covered in traditional medical education. What is the medical student taught, however, about hospital funding and finance, about state and federal laws relating to hospital operation, or about such institutions of growing significance as the nursing home? Will not these matters inevitably involve the efforts of a fraction of physicians?

Medicine and World Health. Lastly there is the role of the physician in world affairs. The World Health Organization, A.I.D., and several privately

endowed foundations have for years been recruiting physicians to dedicate themselves to the amelioration of world health problems. In what form should medical education be best supplied to the many emerging nations? What nutritional resources, not presently utilized, could benefit the presently poorly nourished citizens of many nations? What international or supranational actions could be employed to eradicate many infectious diseases, to curtail the spread of others? Most pressing, what are the medical consequences of increasing world population and how are these to be managed?

An elective course in world health problems is proposed to consider, for and with the medical student, these and other problems. Academic departments of geography, history, economics, government and others, as determined by available talent, might all participate. A kind of internship experience could be arranged by encouraging the interested medical students to spend a free period such as a summer vacation working with health officials in one or another foreign country. The Experiment in International Living has already indicated its interest in possible participation in such a program.

Such an exposure could well prove to be a turning point in the career of a sensitized medical student. Certainly such a career is for the few, not the many, but for those few, notable, important and satisfying activities may be forecast.

These are but a few examples of some of the kinds of benefits that a medical school curriculum might derive from its university associations. Medical curricula are already chronically in a state of revolution. Increasingly the physician will be involved in current events not traditionally part of medicine. In so far as these new responsibilities can be anticipated, they should be met by additions to the present medical curriculum. To provide time for these addenda, an uncomfortable selection of one or more of several alternatives must be made:

1. Delete material presently in the curriculum.
2. Prolong the time dedicated to formal medical education.
3. Demand a higher level of skill and accomplishment of the premedical student.
4. Accelerate the educational process by the use of programmed learning, audiovisual aids, computer-assisted instruction, etc.

The resolution of this quandary is best left for another occasion and another writer.

A New Independent Medical College Seeks the University

Glidden L. Brooks, M.D.

A nagging preoccupation affecting medical practice in the United States for more than three decades is a concern over the growing encroachments upon the traditional freedom and "independence" of the physician. Parallel concern with "interdependence" is becoming manifest among medical schools. Historically, the first general breach in the previously independent status of the medical school was the salutary one generated by the Flexner report and the trends which it triggered.

One such significant trend was in the direction of closer affiliation with universities. This has set the currently prevailing pattern for the development of new schools of medicine as parts of universities. The history and rationale of such a relationship have been copiously documented and effectively established. Furthermore, evidence is accumulating that this relationship is increasing in importance and bids fair to continue to do so in the future. These considerations are, indeed, so compelling as to confront those concerned with the development of new schools with an occasional dilemma—a choice of imposing a premature or unwelcome burden upon an existing university or of coming into being as an "independent" medical school or the alternative of nonexistence. An incipient school, encountering such a problem, must arrive at a solution by attempting to define the medical school-university relationship in terms of needs and opportunities.

Despite the strong trend toward integral university affiliation, there are in the United States seven independent medical colleges and at least two (Mount Sinai and Toledo) are in the process of active development. Among university medical schools there are a number whose affiliation is geographically remote and largely administrative. Such autonomy in academic matters necessarily affects the nature of the "interface" between.

The degree of a medical school's involvement with its parent university varies widely among institutions. It seems a safe observation, however, that most medical schools enjoy a greater degree of autonomy than do other colleges or components of the same university. The circumstances confronting a currently inchoate medical school may serve to introduce some of these considerations.

The Toledo State College of Medicine, on the advice of the Ohio Board of Regents, was established by the legislature as an independent institution. Situated in Northwestern Ohio, the College is flanked by The University of Toledo and Bowling Green State University and is relatively accessible to a number of small colleges of varying size, objectives, and stages of growth. The College of Medicine is firmly committed to the desirability of establishing

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effective academic interrelationships with one, several, or all of these institutions.

Both The University of Toledo and the Bowling Green State University have expressed interest in and support of this concept. The former will become a state-supported school in 1967. Each is currently embarked on a program to strengthen graduate school programs at the doctoral level and is experiencing considerable increase in the size of the undergraduate student body. Bowling Green is predominantly a residential school and Toledo an urban commuter university. The latter includes a College of Pharmacy and a Community and Technical College with current and anticipated two-year programs for subprofessional personnel in the health field.

Unrestricted by preexisting patterns, the independent new school of medicine may develop systems of relationships at multiple interfaces with both of these growing universities, which should be of maximum value to all concerned. To accomplish this, it becomes necessary to identify and examine some of the philosophical and operational elements involved.

An essential ingredient common to collegiate education and medical education is the student. From an immediate and pragmatic viewpoint, colleges and medical schools need communication since one is concerned with placement of qualified graduates in professional schools and the other with attracting suitable candidates for a career in medicine. Geographical propinquity, especially if enhanced by communication, may result in a medical school relying on nearby universities as prime source of students and in the universities looking to the medical school for the placement of the majority of aspiring premeds. Aside from this obvious circumstance, an opportunity exists to explore the recent trend which regards the traditional four years of medical school as an episode (albeit an important one) in the educational continuum in a career which is both scholarly and immediately useful to society. In order to make such a concept meaningful, participation by medical faculty (especially those concerned with admissions) in premedical curricular and counseling functions is desirable. Greater familiarity with medical education on the part of undergraduate college faculty is equally to be wished for.

A possibly more significant aspect of concern for students lies in the area of joint attention to curricula. The logic of the traditional separation for teaching purposes between general sciences of biology, chemistry, and physics and the so-called "basic medical sciences" has become blurred (if not effaced) as a result of a number of recent developments, e.g., students now enter college with better preparation in science and mathematics and, therefore, may be taught at a more sophisticated level; the "knowledge explosion" affecting all the sciences has forced reexamination of course content and objectives; the advent and growth of scientific medicine has led the physician to plumb deeper into fundamentals while the increasing applicability of basic scientific knowledge to clinical problems has lured the "pure" scientist from the ivory tower to his and society's mutual advantage.

In recent years, a number of universities with on-campus medical schools have devoted attention to the interrelationships of premedical and medical

curricula in the basic sciences. An independent school of medicine dealing with neighboring universities does not have the common administrative overlay which presumably fosters such undertakings and, therefore, might be assumed to be handicapped. Actually, the very lack of a single university administrative structure may be translated into an asset, since it permits an administrative pattern to be established which is adapted to this inter-institutional activity. Such an effort, if successful, might be regarded as a pilot program for medical schools (and these are the majority) who draw their students from a number of diverse undergraduate colleges and universities. In this setting a medical college may develop the concept of continuity of educational experience, leading ultimately to the trained physician.

The conditions which have tended to obscure the traditional borders between "fundamental" science and "medical" science do not affect all scientists and all physicians to the same extent. This is only partly a matter of personal inclination and often is conditioned by the degree of specialism encountered. Increase in specialization within the sciences has led to a tendency toward emphasis on one or another aspect of science on the part of university departments and occasionally of whole institutions. The medical school which has access to more than one college or graduate school may seek to utilize what best fits its own needs. For example, the Biology Department at Bowling Green State University is characterized by balanced emphasis on the "classic" approaches to morphology and physiology while its counterpart at the The University of Toledo lays particular stress on the newer impact of molecular biology. The breadth of medical science requires that a student comprehend the fundamentals of both viewpoints. Access to colleagues in both departments on the part of medical school faculty provides the opportunity for obtaining breadth without undesirable duplication and permits remedial programs designed to bring medical students with disparate backgrounds to uniform standard of experience.

Presumably, students have always entered medical school with a variety of prior educational experiences and disparate degrees of intellectual maturity. The intensive, highly pedagogical nature of the traditional curriculum, called "lockstep" by its detractors, has provided a relatively effective means of bringing such a group into phase. This may be partly a by-product of emphasis on memorization, which produced a degree of "informational uniformity" in such a class. The individual student himself provided the integrative factor in his own time and own way, sometimes aided by contrived interdisciplinary sessions at the bedside or in the amphitheater or laboratory. In more than a few instances, the integrative function matures after medical school graduation, during the internship and residency experience.

In the more ventilated medical school curricula of the future (which is now upon us), the need to bring students into phase must present a problem. Closer relationships with undergraduate colleges provide opportunities to anticipate this. To exploit such opportunities, a new independent medical college must attempt to identify its primary "feeder" schools by attention to geographical, cultural, and other populational considerations.

In addition to the obvious and necessary interrelationships in the biological sciences, there are a number of university departments whose subject matter has become increasingly interwoven with medicine in recent decades. A modern medical college is inconceivable without intimate involvement with psychology, both clinical and experimental. Access to medical college facilities and faculty in neurophysiology, clinical neurology, and psychiatry can substantially enrich collegiate studies in psychology.

The term "biomedical engineering" now has a familiar ring and departments with such a designation are becoming commonplace in modern schools of medicine. The application of physical science to medicine can be expanded into a very broad rubric and easily comprises scholarly activities customarily found in university departments of engineering, mathematics, physics, and applied mathematics. If full advantage is to be taken of the growing relevance of such sciences to medical education and research, ready access to interested colleagues in these departments is needed by the medical school faculty and students. These fields, like medicine, are characterized by increasing specialization and a full gamut of these sub-disciplines is unlikely to be found in any but the largest universities. Availability of two growing universities broadens the potential base for parallel development of such activities in the medical college.

Similar reciprocal opportunities for interaction rise from the growth of our society and of our scientific understanding of its nature. A medical college and a university department of sociology, for example, would be hard put to identify a clear line of cleavage between demography and epidemiology. Easy interchange of information, techniques, faculty and students is not only possible in such a situation, but highly desirable. By communion with scholars in the social sciences, including political science and economics, medical students and educators may obtain a more complete and effective understanding of the forces which are destined further to shape the nature and organization of medical practice in the future. These are the forces mentioned earlier as affecting the degree of independence hitherto enjoyed by the individual physician. Scientifically adjoined understanding should enable organized medicine to participate more effectively in channeling these forces toward reasonable social and professional goals.

Medicine deals with a fundamental and comprehensive segment of human experience. If one assumes that familiarity with the nature of man is enhanced by humanistic studies at the collegiate level, it follows that experiences in some depth in history, sociology, literature, the arts, economics, or political organization should be acquired by the physician as a part of his formally monitored learning experience. Medical educators are recognizing that depth of experience in at least one non-science field is a desirable attribute in the medical school entrant. If a continuing scholarly pursuit in the humanities can be made available to the medical student at the level of graduate study, a desirable depth can be added to a base of relatively broad premedical exposure.

The other side of the humanistic coin lies in the advantage a medical school may offer to graduate school students and faculty in the humanities and social studies. Hospitals, clinics, and other health service and educational facilities provide a setting for observation of human life in a variety of situations not otherwise readily available. The role of medicine in history and the role of history in the understanding of medicine is an obvious instance of the type of pursuit which might profitably be jointly undertaken in a medical school-university relationship.

Especially in recent years, medical educators have come somewhat abruptly to face serious problems of pedagogy. Traditional systems of medical instruction have been challenged by such factors as the scientific information "explosion," changes (for the better) in quality of entering students, additions of new disciplines and multitudinous curricular revisions. More and more medical schools are establishing departments or other units for research in the methodology of teaching. Medical education, despite its rather special nature, can draw upon the expertise and research methods in university departments or colleges of education for participation in these activities.

The major avenue of scholarly communion and growth between universities and medical colleges is at the level of the graduate school. Indeed, with the present trend toward independent study and research experience for medical students, this relationship is gaining in usefulness. The place of the Ph.D. degree in medical school faculties is long established, and more recently the desirability of including Ph.D. candidates among the students in medical school has been recognized by more than one-third of U. S. medical colleges. Although a variety of patterns exist, including the award of the Ph.D. by the medical college on the sole recommendation of the medical faculty, arrangements which also involve a graduate school faculty would seem to provide a broader base and enriched resources for studies in depth in medicine-related sciences. The Toledo State College of Medicine proposes to establish programs to include participation at the pre-doctoral level by faculty and students at both neighboring institutions. Since the medical college is new and both universities are developing doctoral programs from graduate programs terminating at the master's level, opportunity for combined academic growth and development is presented.

The administrative considerations involved in relating an independent college of medicine to more than one university are interesting and their final form must be determined by experience. The three schools described are parts of the State system of higher education and, therefore, responsible to a single Board of Regents through its executive officer, the Chancellor. This fact does not significantly abridge the academic autonomy of each institution but does provide encouragement and sponsorship for inter-college experimentation. The pattern evolved may contribute to the further development of medicine as a university function by providing a useful experiment for independent medical colleges and universities unready or unwilling to accept total responsibility for medical education.

Graduate Education and Medical Education: A Synergism

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The initial enthusiasm and humanistic motivation of fledgling medical students, fresh from the liberal arts, are frequently smothered as they are crammed full with anatomical, biochemical, physiological and microbiological minutiae which—in isolation both from the human objects of their studies and from a broad, unifying, intellectually satisfying scientific framework—they soon largely forget. Moreover, the descriptions of stultifying curricula, transmitted from medical students to college undergraduates, hamper the recruitment of high quality candidates for careers in medicine.

The report of a committee of eight faculty members of Harvard Medical School represents the most recent expression of dissatisfaction with the *status quo*. This committee recommended that more time be provided to medical students for independent study and reflection, that the requirements for factual information and memorization be reduced and that, generally, the student be cultivated “in the atmosphere of a graduate school rather than of a trade school” (1, 2). A long record of inertia in many established academic institutions suggests that innovation by renovation may be less expeditious than building totally new foundations.

My colleagues and I believe that the best way to develop the atmosphere of a graduate school within a medical school is through the juxtaposition of two such schools physically, operationally and philosophically. We are currently involved in planning the simultaneous development of a medical school and a graduate school of biological, behavioral and social sciences. These coordinated schools will be built onto the plant of a voluntary hospital steeped for more than a century in a tradition of excellence in patient care, community service, scientific research and teaching. We are contemplating in broad outline a two-track program for college juniors and seniors who are seeking careers in medical practice and/or in medical and biological research. There will be a single, high standard for admission, but we anticipate that approximately 80 per cent of our students will choose to follow a medical core curriculum consisting of an intimate interweaving of formal courses in basic, behavioral, clinical and social sciences with early direct exposure to patients. The remaining students will follow a more intensive and broader core of basic science lectures, seminars and laboratory work in the graduate school.

The two tracks need not always diverge and, indeed may often converge so that all courses as well as extensive tutorial opportunity can be available to every student. For example, the medical and graduate core curricula will overlap

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considerably (i.e., entire courses in subjects such as biochemistry and physiology may serve in both curricula). Some of the subjects which are required on one track (i.e., pathology in the M.D. core, some aspects of evolutionary biology in the Ph.D. core) will be available as electives for students on the other track. The option to switch tracks will be available to first and second year students whose interests have changed, provided that their academic performance has been of high calibre.

Thus we hope to achieve vital interdisciplinary interactions among clinicians, basic scientists, medical students and graduate students—within one institution and within either a single building or a compact campus of adjoining buildings. In contrast to prevailing trends, a sophisticated command of most of natural science will be expected of all of our Ph.D. candidates, while many of our M.D. candidates will be permitted to sacrifice breadth for clinical and/or biological depth. Some unusually motivated and able students may earn both the M.D. and Ph.D. degrees. Inasmuch as the final orientation of each student—on the basic-to-applied spectrum—will be determined by his intrinsic capabilities and maturing interests, we believe that this plan should diminish the tendency “to produce researchers *rather than* physicians” (1, 2) in favor of a tendency to produce *both* physicians *and* researchers.

Although it has long been recognized that a professional school functions at its best when it is broadly and deeply involved with its nonpragmatic counterparts within the university, effective ties between the professional and the “pure” elements of modern higher educational institutions have been limited. To be sure many medical school departments make use of the administrative apparatus of their university's graduate schools for the formal processing of candidates for the Masters and Ph.D. degrees, but there is generally little substantive or inspiring academic interaction. In effect, each school operates autonomously, the basic science departments of the medical school having little or no influence on the biology and chemistry curriculum of the graduate school (or the undergraduate school) and vice versa (3). There are, nonetheless, many reasons for believing that cross-fertilizing and productive ties between medical and graduate schools can be achieved if the two units are developed contiguously with curricular, scholarly and laboratory interaction established from the outset.

Douglas Knight (4) describes eloquently the fundamental responsibility of graduate schools of arts and sciences:

They are not primarily obligated to a profession, but to a discipline; and they build their relationships of knowledge, wisdom and action in ways that superficially seem more tangential to life than those of the professional schools. The vigor and significance of a great graduate school express themselves most clearly in a power of self-criticism, in a constant dialogue between what is known and what may be known. To put it another way, the constant critical evaluation of knowledge is the major task of a graduate school; only out of it can come the two formal achievements which justify having such schools as one major part of a university.

The first formal achievement, of course, is the extension of knowledge; and knowledge is only extended effectively under a constant structure of criticism and revalu-

ation. The random extension of knowledge means nothing until it is caught up by a mind of creative power; it is not too much, indeed, to say that knowledge becomes real only at that point. The second formal achievement of the graduate schools is the education of future scholars; and here too we must realize that training which limits itself to the manipulation of dead learning has no real value. The scholars of the future must be even more critical and creative than the scholars of the present. They must be so precisely because they will also have to be more learned, and their learning will bury them unless they have *within their graduate discipline itself* the means of ordering, controlling and valuing what is known.

If creative learning at its best involves this constant and critical dialogue, it does not stop there. Often it may look as though distinguished scholars talked only to themselves and one another; but they also carry on a constant conversation with their society. The thought of a Newton or an Einstein is first of all a conversation for two or three minds; before it is finished, however, it has shaped national action and the inner lives of countless human beings. In a hundred less publicized areas, the scholar changes our world. He may bring forty years of learning to bear on the Dead Sea Scrolls; he may interpret for us the inner life of a Lee, a Jefferson or a Lincoln; he may show how the obscure passages of Proust or Joyce represent some of the most penetrating and necessary insight of our century.

In all these matters, the true scholar maintains a precarious balance. He fails if he tries to make his insight constantly useful to the society around him, because he inevitably falsifies it; and he fails equally if he adopts the position that the more esoteric and unavailable his learning is, the more glorious. It may simply be dead instead. What the scholar has to offer his world is some calm sense of the relative importance of its various preoccupations. He affects its action by the sharpness of his interpretation, and by the courage with which he supports his insight. In this way he is a profoundly active person himself, of a less spectacular and yet often a more abiding sort than those whom we usually deify as our heroes of action.

Surprisingly, as the total number of scholars in society increases, fewer seem to fit this ideal—the burgeoning of information makes it more difficult to achieve depth in a specialty and at the same time to develop and retain breadth throughout the full range of science or even within the confines of a single discipline. A *typical* graduate student today is allowed or even encouraged to limit his development as a generalist in favor of virtually exclusive concentration within a subdiscipline and thus, Ph.D. notwithstanding, he emerges from school with a perspective of such narrowness as to rob him of the ability to make the important value judgments which should set the course of his career, insure the development of his own students and ultimately affect the nature of the society in which he lives. In the laboratory his interests and activities tend to move toward greater “purity” within his elected discipline and greater remoteness from other disciplines. He is, therefore, likely to address himself to the more readily soluble problems that arise within a single discipline rather than to the less tractable but more “important” problems which tend to bridge disciplines and require a breadth of background and experience which he has been denied. Thus he may be forced into a sterile commitment to minutiae which he may rationalize in the name of *l'art pour l'art*.

The medical student or physician may find himself in an equally unproductive intellectual abyss because of comparable narrowness of perspective at the

pragmatic end of the spectrum. Thus the responsible educator is faced with the problem of deciding how best to respond to the pressing needs of modern society and yet to preserve both for his students and himself "a leisurely and urbane attitude toward scholarship, exemption from the [overriding] obligation to use knowledge for practical ends, a sense of perspective which accompanies the broad horizon and the distant view, [and] an opportunity to give undivided loyalty to the kingdom of the mind" (5). The roots and ramifications of this problem are developed in Alvin Weinberg's discussion of the incongruence of our "mission-oriented" society and our "discipline-oriented" universities (6).

I believe that it is important to face the "mission-discipline duality" in medical and graduate education by attempting to develop scholars in both the clinical and basic sciences who can maintain the "precarious balance" between "application" and "purity" on the one hand and "specialization" and "generalization" on the other.

As a first step toward the realization of this goal, I would like to see a broad interdigitation of graduate education and medical education in which faculty members and students (whose intellectual and motivational orientations cover the full range of the "mission-discipline" spectrum) would have close contact in a set of core courses, portions of which would be given to graduate and medical students together. Under consideration in this context are the following courses: Morphologic Preparation for Experimental Biology; Principles of Biochemistry and Biophysics; Physiology of Cells, Organs and Organisms; Introduction to Mathematical Methods; Microbial and Molecular Biology; Genetics and Evolutionary Biology; Developmental Biology; Introduction to Behavioral Biology; Selected Topics in the Philosophy of Science; Colloquium on the Linkages Between Science and the Humanities (7). That portion of each of these courses for which both medical students and graduate students would be held responsible, i.e., the "common core" material, would be limited to major definitions, principles and processes. The medical student group would be held responsible for a "core increment" of additional subject matter which would be available for audit or elective work by the graduate students. Similarly, graduate students would be held responsible for a different "core increment" which would be available for audit or elective work by the medical students. In addition to the "common core" and "core increments" there would be an extensive list of purely elective course and seminar offerings (7) in which graduate students, medical students, postdoctoral fellows and faculty may further advance their studies and at the same time form new associations or continue previous associations established in the common core courses. Seminars on the relationships among physical science, biology, medicine, social science and the humanities would be held jointly by the medical and graduate schools throughout the academic year for all classes of students and all members of the faculty. Opportunities would be provided to senior medical students to explore experimental or theoretical problems in depth within the graduate school. In se-

lected cases, where educational experimentation seems justified by interest, apparent research potential and personality, a medical student would be encouraged to spend a summer or an elective period working full time with an advanced graduate student as the latter reaches a crucial phase of his thesis research. Such an association would be closely supervised by the graduate student's thesis sponsor and the other members of his faculty advisory committee.

In addition to the scheduled points of contact between graduate and medical students and faculties, informal association would be facilitated by common library, dining and recreational facilities.

A comprehensive blending of medical and graduate school activities within a single institution is a necessary first step toward an even broader association of educational resources involving several institutions. I have been involved for several years in the development of a formal interinstitutional program in graduate and professional education which my colleagues and I plan to implement when our first group of graduate students matriculates. The impetus for the development and implementation of this program derives from the general recognition of the shortage of outstanding faculty and facilities relative to the needs of professional and other schools within most, if not all, universities; thus, no single institution is likely to retain teachers, scholars and scientists who are all of the highest calibre. Without compromising the integrity of any participating institutional unit, this program seeks to cut through the tradition of self-containment that limits the offerings of even a superior university to those of its own faculty and facilities. It defines a *modus operandi* by which a school can circumvent arbitrary barriers of distance and permanent affiliation and thereby render its "enveloping membrane" permeable to the best influences in the scholarly and scientific community. It assumes that key educational (and para-educational) institutions can benefit greatly by sharing facilities, personnel and administrative apparatus in carefully selected, mutually sponsored teaching and research activities. I believe that such an association can create a unique educational opportunity capable of attracting and benefiting outstanding students, and that the augmented quality and quantity of interactions among a broadened faculty and a stimulating group of select students can provide a new and vital format for higher education of gifted students in the life sciences as well as in other disciplines.

Specifically, the program will offer to gifted predoctoral students the combined faculties and facilities of our graduate and medical schools, one or more research institutes (such as the Brookhaven National Laboratory) and, hopefully, one or more universities. The first phase of training will consist of the tutorial, course and laboratory work of our graduate "core" program and, in addition, supplements from our elective program (7) and/or from the programs of other participating institutions. In general, the student will be expected to complete the period of formal study and to pass a preliminary qualifying examination before final arrangements are made for sponsorship of

his thesis research. Each student will then select his thesis subject and sponsor with the guidance and approval of a committee of graduate faculty advisors.

During the initial years of formal academic work, the teaching effort of our graduate faculty will be augmented by the participation of a small, select group of visiting professors. When the period of formal course work has been completed, thesis research may be carried out in any department of any participating institution in which suitable space and sponsorship are available—although most of the students who take our “core” program would probably remain on campus. Under special circumstances, students may be permitted to conduct thesis research abroad in the laboratories of foreign members of our visiting faculty. The final evaluation of each student’s overall performance will be made by his thesis advisor in conjunction with a committee of senior graduate faculty members, and the degree will be awarded by our graduate school. Reciprocal arrangements would exist for students who take their initial course work in other participating graduate schools.

This program should bring about an increase in the vitality and effectiveness of the participating institutions. More generally, the program presents a means for increasing the utilization of the most critical educational and scientific resource—manpower of proved excellence—and it formalizes a new approach in graduate education whereby, through relaxation of excessively-restrictive academic sovereignty, it allows cooperating institutions to enrich their resources by sharing them. For the teacher and researcher, it offers the stimulating and satisfying experience of interaction with select students and superior colleagues; for the gifted student, it offers a broad and inspiring preparation for a creative scientific career; for society it establishes a new pattern of educational organization whereby graduate schools, professional schools and research institutions associate for mutual benefit and achievement.

In conclusion, I believe that a close working association between a medical school and a graduate school is important for the recruitment of basic science faculty members of the highest quality, few of whom would be willing to sacrifice the stimulation and satisfaction of working with graduate students. Moreover, such an association can bring to the institution as a whole a major expansion of teaching strength, research productivity and general intellectual scope. It can also provide an intellectual and humanistic climate in which interactions between mission-oriented activists and discipline-oriented theorists bring about a salutary blending of the pragmatism of the former and the purism of the latter—so that all can relate their evolving interests and growing competences to the pressing professional needs as well as the loftiest intellectual ideals of our society.

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An Integrated Program for Premedical and Medical Education—Its Impact on the University

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Advancing knowledge in medicine and the medical sciences, the growing importance of concepts and approaches of the physical sciences and mathematics to an understanding of living systems, and the remarkable changes occurring in secondary education call for the broadest possible considerations of the total educational program for the physician. It is no longer appropriate to be concerned only with the small segment of the program represented by the four years of medical school. This urgent need was recognized by a group of faculty at Northwestern Medical School who were asked to propose changes in the medical curriculum. Because of their concern, discussions were undertaken with faculty members in other schools of the University. These led to the appointment of a University Committee on Medical Education with representatives from the College of Arts and Sciences, the Graduate School, and the Medical School.

Although the Committee recognized that ideally the problem called for overall consideration of premedical, medical, and house-officer training, it focused its attention on the first two segments of the traditional educational program for the physician. These segments are primarily controlled by the University, although some outside influence is exerted through accreditation and licensing boards; house-officer training is more directly dominated by requirements of the specialty boards, which are essentially extra-university.

The following aims and purposes were adopted early in the course of the Committee's labors: (1) to eliminate the present sharp division between premedical and medical education, (2) to introduce at the college level materials of study that have a more direct bearing on the study of medicine than are available in the conventional premedical program, (3) to continue into the professional curriculum relevant studies which are at present presumed to be available only in the college curriculum and which are not directly related to education for medicine, and (4) if possible, to reduce the length of time required for the completion of the course of study.

In devising a program of education consistent with these aims and purposes, the Committee soon became aware that a single solution for all students desiring to prepare themselves for medicine was neither desirable nor possible. Although medical students come from the upper levels of high school graduates, they nevertheless exhibit a considerable spectrum of background

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and ability. A decision was made to concentrate efforts on a program for the most promising students prepared in the most advanced high schools. It was felt that the program would probably have a salutary effect on the educational program for all levels of students and could later be broadened as experience was gained. Furthermore, a challenging and exciting opportunity might reduce the loss of the most capable students to other disciplines.

It has not been necessary to revise, to any important extent, the concepts developed by the Committee in order to implement the plan. These are described in considerable detail in an earlier report (1) and will not be repeated here. The planning was facilitated by a John and Mary R. Markle Foundation grant, which permitted faculty members to devote substantial time to the project, and by consultation with outstanding educators from other institutions. The implementation of the program was made possible by two generous grants from the Commonwealth Fund. This support allowed faculty members to devote full time to the development and presentation of special courses both in the College of Arts and Sciences and in the Medical School.

Students are admitted to the Honors Program immediately after graduation from high school. A minimum of two years is spent in the College of Arts and Sciences; about one-half the curriculum consists of required courses in the sciences and the other half in electives in the arts, humanities, and social sciences.

The science sequence includes courses in physics and mathematics, chemistry, and the biological sciences and is not narrowly designed for immediate applicability to medical science. Each of the sciences is represented by a demanding and mature course which stresses the general concepts and the approaches of its particular discipline. The math-physics course presumes some high school training in calculus and carries the students into differential equations. A one-quarter course in general chemistry and a two-quarter sequence in organic chemistry complete the science curriculum of the first year. In the second year, students are enrolled for two quarters in the course in physical chemistry ordinarily taken by junior or senior chemistry majors, and for the third quarter in a special course which stresses kinetics. In the second year, students also are enrolled in a three-quarter sequence in biology. This course is heavily oriented toward the quantitative aspects of living systems. The first year at the Medical School serves to round out the considerations of basic biology. Thus, an integrated sequence of science training has been achieved with each separate course relying heavily on the knowledge provided in previous courses and leading logically into the content of subsequent courses.

Students admitted to the Honors Program are generally given advance standing in English, history, languages, and social studies. Thus, in the two years of residence in the College of Arts and Sciences, Honors students achieve junior level in many courses. Training in humanities is continued in

the Medical School part of the program. During their last four years, Honors students are required to register for five seminar courses in the humanities from among about twelve offered at the Medical School by distinguished members of the College faculty.

The quality of its students is undoubtedly the most important ingredient of the Honors Program and insures its continued success. Their talent and dedication attract and hold the interest of the faculty and make feasible the realization of otherwise conflicting aims of more rigorous training in the sciences and a reduction in the allocated time. As mentioned above, students are accepted during their senior year in high school. Selection criteria include objective data such as class rank and scores on Scholastic Aptitude and Achievement Tests and on the National Merit Scholarship Qualifying Test. In addition, recommendations from high school teachers and administrators are carefully evaluated, and the commitment of the high school to honors courses and the participation of the student in such courses is determined. Almost all applicants retained after preliminary screening are interviewed by representatives of the College and of the Medical School. The overall average for the Aptitude and Achievement Test scores has been over 700 each year; the National Merit Test scores have averaged about 146; and, for the past two years almost half the accepted students have been at the very top of their respective high school graduating classes, and the remainder have been in the top 2 or 3 per cent.

Scholastic performance of Honors Program students during their two years in the College has been excellent for the most part. The science teachers report that working with this group is an enormously satisfying and challenging experience, and the prediction of early critics that the science faculty would be unwilling to participate in special courses has proved to be grossly incorrect. On the contrary, the teaching of the required science courses is considered to represent a particularly desirable assignment and, in fact, has been used as an inducement in recruiting new faculty members.

In spite of great care in selection, two or three students out of the twenty-five to thirty selected each year have encountered serious scholastic problems. Assuming that all of the students have already demonstrated their ability for high scholastic achievement, one must conclude that the selection procedure is less than perfect and that the Honors Program does not provide an intellectual environment in which all talented students are able to flourish. These conclusions may appear to be trivial but the problems and observations which led to them were unanticipated. The few students with scholastic problems are not abandoned but, on the contrary, remain an important responsibility of the Program directors and of the University. They are carefully studied, counseled, and led ultimately into more appropriate academic areas. The percentage of "rescues" has been gratifyingly high.

A few students each year change their minds concerning their ultimate careers and decide on some field other than medicine. Consequently, the

Program has provided excellent students for a number of other schools and departments in the University and simultaneously has been able to help such students find the educational experiences they seek.

Approximately 80 per cent of the initially accepted students formally register in the Medical School at the end of the second year. Three groups of Honors Program students, at the time of this writing, have moved from the College to the Medical School, where they have joined the balance of their respective medical classes, composed of students who have had traditional premedical training.

Although it is not employed for selection purposes, students in the Honors Program are asked to take the Medical College Admission Test at the end of their second year, just prior to registration in the Medical School. In each category and without exception, the Honors students have achieved scores higher than those of their classmates, in spite of the fact that they have had only two years of college while 80 per cent of the traditionally trained students have had four years of undergraduate education. The scores of the Honors students average over fifty points higher than those of the others.

Average performance of the Honors students in the Medical School is detectably better than that of their classmates and approximately two thirds are in the upper half of their classes. Honors students are always found among the top ten students; and in one of the three classes, six of the top ten are members of the Honors Program.

The Honors Program has had and continues to have far reaching influence throughout the University. It is probably the only activity of the Medical School known by virtually every member of the University faculty and it has created a cooperative interaction between the Medical School and the College of Arts and Sciences. This is particularly important to Northwestern University, where the Medical School is separated from its parent institution by about a dozen miles and, as a consequence, where intellectual isolation tends to develop unless explicit programs are designed to involve both campuses.

A number of curricular changes in the College may be traced directly to experiences provided by the Honors Program. The first three Honors classes received a specially designed course in biology, one which, as outlined above, was designed for students with particularly good training in chemistry and mathematics. Success with this course led the faculty of the Department of Biological Sciences to revise completely the curriculum for biology majors. These students, like the Honors Program students, are now required to take chemistry and mathematics during their freshman year and they then begin a six-quarter sequence in modern biology in the sophomore year. Accordingly, a special course in biology is no longer required for Honors Program students, who now take the first three quarters of the six-quarter sequence before moving into the Medical School for further training in the biological sciences. The Chemistry Department has adopted the one-quarter introductory course for many of its highly qualified majors in place of the two-quarter honors sequence previously offered.

Not only has the Honors Program been the stimulus for curricular change in the College of Arts and Sciences, but the presence of Honors students, with their unusual talent and training, represented a challenge in response to which the medical faculty instituted important changes in its teaching program. The first year of the Medical School curriculum is completely new, both in concept and in operation; and the second year has been significantly modified. The new curriculum, without sacrificing the regular medical students, takes advantage of the rigorous science training provided for the Honors students and tends to diminish the discontinuity between the programs in the Medical School and the College. Thus, the medical students now take a multidisciplinary course in cell biology which is based, in part, on the biology and chemistry courses taken the previous year. Cell biology is followed by multidisciplinary courses in such areas as tissue biology, microbiology, and immunology.

The implementation of the Honors Program created the probability that the number of Northwestern students seeking careers in academic medicine or in combined medical research and practice would increase. Accordingly, considerable time and effort have been expended in organizing a new program to meet the needs of such students. This program has undergone rather extensive annual change and currently consists of a special combined curriculum of medical and research training into which Honors students are admitted at the end of their second year, at the time they move to the Medical School campus. Honors students who elect this course of study necessarily expand their time commitment from six years to a total of eight or nine years, the last six or seven of which they are in residence each of the four quarters of each year. At the completion of the program they will have earned a Ph.D. degree as well as an M.D. degree. This program was one of the first of three combined-degree programs supported by the National Institutes of Health.

The most important impact is one which cannot be stated in terms of tangible innovation, such as new courses or revised curricula. The successful conception and implementation of the Honors Program has served to create an atmosphere of inquiry and ferment and to loosen the hold of traditional and time-worn educational methods. A close interaction between the Curriculum Committee of the Medical School and the administration of the Honors Program has resulted in the study of extensive and fundamental modifications in premedical and medical education at Northwestern University. It has stimulated further attempts to construct a rational and coherent educational experience sufficiently structured to provide rigorous training for modern medicine but sufficiently flexible to meet the needs of a student body with a spectrum of capabilities and ambitions. It has brought about reexamination of the undergraduate programs in science in the College of Arts and Sciences and has furnished an important link between the two campuses of the University. Through discussions, the faculty has a better understanding of the needs and challenges offered by educating bright students in the life sciences.

PROBLEMS OF NEW MEDICAL SCHOOLS, HERE AND ABROAD

Medical Education for Tomorrow

William F. Maloney, M.D.

Change is the continuing challenge of our century. Sir William Osler must have sensed that this would be the characteristic of the new era when, as the century opened, he observed: "This is yet the childhood of the world." He was perhaps the first, though not the only modern medical educator, to be aware of the fact that, if the world was still in its childhood, medicine and medical education would be in their scientific and pedagogic infancies.

The whole history of medical education since Osler's time demonstrates that, like the rest of science—indeed like society itself—change is the one constant upon which thoughtful men may rely. Thus, it has been wisely said that our only certainty of today is the uncertainty of tomorrow.

Whether one welcomes or abhors change in medical education, it must be faced that the times require new methods and new approaches competent to meet a variety of new social and scientific needs in medicine. It is a welcome circumstance, therefore, that at least fourteen new medical schools are now in process of gestation and birth in this country. They will be less encumbered by the inhibiting influence of vested interest and by the dulling effect of the comfortable old ways. They will inevitably generate more innovative approaches for dealing with current trends. In an earlier time, a certain rigidity of standardization was necessary if medical education was to achieve even minimal scientific and educational recognition. That was prior to the famous Flexner Report of 1910. Until then, there had been variation in American medical education, but the differences were, regrettably, of quality rather than of method. Flexner's report urged medical educators to adopt goals and standards far superior to those, with a few notable exceptions, in force at that time.

The country's educators responded admirably, imposing upon their medical schools a system of self-policing that raised them to an acceptable level of competence throughout the nation. Inevitably, however, our schools were bound by rather rigid standardization. An uninspiring uniformity resulted and lasted for more than a quarter century.

In the past twenty-five years, however, and especially in the 1960s, an exciting diversity both of program and of philosophy has begun to pervade

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medical education. This change is a response to the forces inherent in our increasingly complex society. The medical institutions of the United States and the agencies responsible for guarding educational standards can justly take pride in having freed themselves from the necessary rigidities imposed by an earlier more primitive state of affairs. Accreditation procedures were once not unlike police actions. Today they more closely resemble consultative discussions between colleagues. Institutions have been encouraged to depart from traditional approaches as they seek to solve novel problems or to improve upon older ways of teaching. As a result, this decade has seen a healthy and important increase in the number and variety of experiments in medical education. The variation is now characterized by consistent good quality.

The following account of trends in medical education is essentially a projection. As such it describes the changes we can now observe, but inevitably it also progresses into territory less well mapped: to forecasts of what could happen and even to such presumptuous speculations as an estimate of what, perhaps, should happen. In doing so, however, it is consistent with the thought of others, particularly that reported in "Planning for Medical Progress Through Education." The report was commissioned by the Association of American Medical Colleges from a committee of highly qualified experts and was written by Dr. Lowell T. Coggeshall.

Today medical education faces many critical problem areas. Four appear to be pivotal. They reflect forces in society that are compelling change in objectives, curriculum content, methods of teaching and in the medical school's role in society. In examining the impact of these forces, focus is for the most part upon that phase of medical education leading to the M.D. degree.

The distinction between this phase of medical education and postgraduate education is as delicate as it is crucial. It is the difference between responsibility for planting and nurturing germinal growth and that of adding refinement to the maturing years. It is the difference between shaping and polishing. Just as the parents' responsibilities and opportunities are greatest in the child's earliest years, so are the teacher's responsibilities and opportunities greatest in the medical student's years. They constitute the formative period, the time when he develops his concepts and attitudes toward his profession, his colleagues, his patients, and toward learning, science, and society as the triad of his professional concerns.

The first of the forces referred to is the scientific information explosion. The volume of knowledge that is essential to medical practice or medical research long ago reached the point where it had to be subdivided into learnable segments. Medicine's response to the information explosion has been to specialize in an attempt to survive the flood of accumulating scientific knowledge that threatens to inundate the educational enterprise. The result is a paradox: multiplying knowledge forces the individual into more and more restricted areas of professionalism; yet at the same time society increasingly demands breadth of understanding of the interrelationships between the specialities.

These problems are compounded by the fact that the biological sciences are today approximately where the physical sciences were before the discovery of the laws of thermodynamics, atomic structure, and quantum mechanics. Biology, particularly human biology, remains largely an unorganized mass of data. Detail and fact are yet to be related in some integrated system, but unity is appearing. The cornerstones of fundamental biological law are now being laid. Genetic mechanisms, for example, are common to all life. The ultrastructural characteristics and metabolic mechanisms of the living cell are likewise basic to all forms of living matter.

Selecting the most useful and the most significant information from the masses of data available remains extremely difficult, however. In human biology and in medicine this task is a responsibility of the medical school. It must assist the student to understand the basic concepts and principles and to apply these to his widening professional interests.

As the schools meet that responsibility, some new interrelationships and interdependencies of subject matter are already apparent. It appears that the accumulated knowledge should be organized and taught by biological systems, carrying them progressively from their most primitive to their most complex levels of structure. Such a reorganization of material offers the student a better opportunity to correlate and integrate his knowledge than does the traditional curriculum based upon disciplines and specialties. Moreover, it is more adaptive to the needs of modern scientific and social life: Where once it sufficed to conduct what has aptly been called "undergraduate medical education," only genuinely graduate-level study aimed at making of the student a scholar and, in consequence, the doctor a scientist will now meet today's needs.

The older pattern of undergraduate medical education organized its courses traditionally as; anatomy, pathology, physiology, biochemistry, medicine, surgery, pediatrics, obstetrics, gynecology, etc. This no longer is sufficient. Several schools are now offering the student the opportunity to study in integrated fashion such topics as cell biology, tissue biology, and whole organ systems; for example, the cardiovascular, the nervous, the hematopoietic. Fortunately for the medical schools, the increasing depth and comprehensiveness of secondary and college education in this country today have made their tasks easier.

The basic sciences are beginning to be taught at these levels with sufficient sophistication to permit the medical schools to reduce the curricular time devoted to elementary understanding of such subject matter. The time saved will allow the student to electively acquire knowledge in depth in selected subject areas. Thus, schools can also include for study the complexities of man as a social organism.

It has been demonstrated that such a curriculum can be determined, organized and taught effectively by interdepartmental groups. Subject matter can be presented system by system from the molecular through the cellular,

tissue, and organ-system levels to the functioning of the organism as a whole in the context of his modern and primarily urban environment. Such an interdepartmental approach does not, as some feared, impair the administrative and scientific functional efficiency of the cooperating departments nor their ability to provide a program of graduate education in their discipline. If anything, it has the fortunate effect of broadening the perspectives of many whose concentration upon their specialties would normally tend to limit their horizons.

This brings us to the second pivotal problem area of medical education today: the art and science of teaching and learning. No matter how ingeniously organized, a curriculum must be well taught by individual teachers. In the past, medicine has assumed that the M.D. was also a degree in education. Pedagogical theory and practice were too often regarded with disdain and considered irrelevant to the problems of medical education. Such an attitude may have been appropriate to the vocational or professional-school concept of medical education, but it is wholly unsuited to an approach that renders the medical school an authentic graduate school of a university.

Today, the members of a university faculty of education are recognized as the colleagues of medical educators. We have much to learn from them in developing new teaching and learning theories and methods for our medical schools. Innovations are the order of the day. Small group and seminar teaching are more and more common. The research project increasingly is replacing the repetitive laboratory experiment. Sophisticated audiovisual aids, the use of television, particularly as a tool for bringing the student into intimate, "close-up" contact with clinical events, programmed instruction, study cubicles, and other modern teaching devices are being introduced.

The multidisciplinary laboratory is proving a particularly useful and effective teaching mechanism. It meets the need to expose the student to a many-faceted approach to his subject matter. Used in conjunction with sophisticated learning theory, such laboratories enable students to integrate their knowledge and bring it to bear upon the problem at hand.

Such techniques and devices are useful only to the extent to which they support the basic teacher-patient-student relationship of medical education. They must therefore be chosen to fit the particular pedagogical need. Mere innovation for the sake of innovation is pointless. However, a methodology and its corresponding technical equipment designed for modern multidisciplinary teaching may enable us to increase the size of our health manpower force despite a shortage of good teachers.

The third force powerfully influencing medical education today is research. Medical care is based upon the artful application of scientific principles to the pathology at hand. From this fact arises an exquisite interdependence of research, clinical practice, and medical education. One learns by doing. Medical students learn at the bedside, but they must also learn in the laboratory. At the former they learn what it is to be a physician; at the latter, what it is

to be a scientist. In this way research forces the student to develop objectivity, sharpens his capacity for critical perception and dispassionate judgment, and provides him with the scientific method as a pattern for solving problems.

Of late there has been renewed appreciation of the fact that the art of healing is not the same as the science of medicine and that emphasis on the art of healing in medical schools has not been sufficient. Several schools, and new schools in particular, are taking cognizance of the fact that scientific knowledge must be applied by human beings to the problems of other human beings. Hence, the interpersonal relationship between doctor and patient always stands as a potential major therapeutic force. There is also a new emphasis on another set of the patient's interpersonal relationships; his relations with his family, his friends and with the community and its physical environment. The importance of considering all of these elements and of utilizing them in a positive manner in restoring the patient to health is more and more recognized as vital to the student's future role as a physician and as a key member of society.

These developments are bringing medical schools toward a total commitment to total medical care. This is in large measure an appropriate response to the multiple pressures that society consciously brings to bear upon medicine. Social forces, then, are the fourth group of problems with which medical education must reckon.

Medicine itself has done much to bring about this change. In Osler's day, the chance of cure for a patient chosen at random was relatively low. Today the picture is very different, and, in consequence, society's demands are very much altered. Health is no longer a prerogative of wealth. Our democratic society regards it as a basic right. By no accident, the capacity both of medicine and of our social organization to meet these demands has also significantly altered. In Osler's time, what was impossible is today perhaps difficult, but attainable. Both the social and the scientific reality, in other words, have radically changed in the past half-century, so that today we can predict with confidence the possibility of maintaining the health of virtually the whole population from conception to old age.

Responding to these changes, medical education should reexamine the crucial element—the educational environment. The teaching of medicine differs from other disciplines in this vital respect: it must always teach by precept. The medical student learns by example, never by rote, and so he can only learn by actually caring for patients and by actually conducting research, never by merely listening to descriptions of how patients are treated or how research is conducted. This means that the environment for learning should include most of the elements that the future physician will encounter in medical practice and research. It should include the whole range of types of medical care and medical care systems prevalent today and tomorrow.

Most of our medical schools do not provide such an educational environment for their students. New dimensions to be added include the full range of preventive and restorative functions in medical care, the complete spectrum of deviations from health, and the experience of furnishing continuing care

from first contact and first appraisal forward to restoration and maintenance of health.

Such an environment should be designed primarily to satisfy a demonstrable requirement in today's complex medical system; the need to assure medical care of uniformly high quality commensurate with the advanced level of today's medical science. It should also satisfy a second need; the need to provide for the individual, within the context of his family or social group, a logical entrée into the medical care system so that continuity and comprehensiveness of care are assured by making available to him the optimal combination of services of medical specialists and other members of the health-care team that his particular condition requires.

It is unrealistic to demand that medical schools teach this kind of medicine without the environment essential to its demonstration. That environment must be created by the conscious decision of our schools to take responsibility for family and community care. Responsibility for acute care in the hospital has long been a part of our tradition. Today it must be extended. It is to be hoped that at least some schools will provide models for that endeavor by incorporating a population group as part of their total responsibility. To do so effectively, they will have to assume the continuing care of a representative cross-section of a population and furnish health care to it throughout the conditions of everyday life.

If such concepts are to be given reality, however, some preliminary steps are needed. Our centers of medical education, the practicing medical and health professions, and our community leaders must achieve a common ground upon which they can work together. Well planned research in the modalities of providing medical care can provide this common ground. It can also provide the momentum and the sense of direction required if the resulting changes are to be progressive and consistent.

That such an effort to evolve a philosophy of modern medical care and a congruent medical curriculum is already under way, this volume is an eloquent witness. The thoughtful reader can hardly conclude otherwise than that our medical academicians are both willing and able to meet the challenge.

Challenges to New Medical Schools

J. R. Ellis, M.B.E., M.A., M.D., F.R.C.P.

The purpose of a Medical School, new or old, is to educate young people in medicine so that they may, after graduation, be trained in some particular branch of medicine. This has not always been the case. In the past schools could produce fully trained general doctors, and there is still a substantial body of opinion to the effect that even now a medical school in a developing country should aim to turn out (at least after a compulsory year of internship) general doctors ready for independent practice. Unfortunately there is overwhelming evidence that this view is seldom shared by the graduates themselves. In countries where many new medical schools have been established in recent years, but where scant provision for postgraduate training has been offered, the graduates emigrate in large numbers to countries where further training is available.

For many well known reasons which do not need reiteration medical education has become a process of education and training of which only one part can be completed in the medical school. It is to a very vital extent concerned with preparing the individual for a rapidly changing future while teaching him what may be described as the grammar of medical practice. As change is likely to be even more rapid in a developing country than in those more advanced it is particularly important that its young doctors should be adequately prepared to face the future, especially if they are to work as general practitioners. Inevitably they will be few in number in relation to the medical need and will have to act as leaders and consultants to a team of nonmedical personnel who will have received only short, intensive and specialized training.

The more advanced country is already better (though seldom sufficiently) provided with consultants and specialists. It is consequently better able to carry "general doctors" who can each provide quick personal service, guidance and comfort for two to three thousand people, but are limited in their ability to make much positive interference in the course of disease. It is becoming clear, however, that this is a temporary situation. As the work which can only be done by centralized teams demands an ever increasing number of the medically qualified it is increasingly difficult to spare doctors for a personal first-line service or persuade them to engage in this type of work. It would seem, therefore, that in all countries the emphasis in the next quarter century at least will be upon establishing adequate centralized medi-

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cal services. The provision of a thinly spread screen of medically qualified personnel for the immediate comfort of small groups of population will be seen as a luxury which none can yet afford.

These trends are now clearly visible in most of the more advanced countries, either as the result of uninhibited evolution or of planned development. In the United Kingdom, one of the strongholds of the general doctor, the two changes required to make him more effective can be seen progressing synchronously—his withdrawal from peripheral isolation to a more central group on the one hand and the provision of a specialized postgraduate vocational training for him on the other. The corollary of course is the abandonment of any attempt to use the medical schools as factories for the production of ready-use doctors. This adaptation of medical education to contemporary medicine in the more advanced countries is of far reaching importance, for at least it begins to indicate to the developing countries the sort of medical education they must offer if they are to avail themselves of the medicine of today—which is after all what they both want and need. It becomes at last apparent that medical education is as much a matter of an “internship” and “residency” as it is of a “medical school period.” It follows that countries with no medical school at all are none the less engaged in medical education even if their young nationals graduate in foreign lands.

Postgraduate training must be as closely associated as possible to the needs of a particular area. Its concern is to teach the current techniques needed in that area—the special vocabulary of medicine. It may be that training in certain necessary techniques cannot be provided in a particular country and a man may have to go elsewhere to obtain it. He can, however, learn how to deal properly with his own people only in his own land and some part of his training must take place there, during which time he will render a much-needed service. Economically it is obviously unwise for a developing country to concentrate upon the first or medical school years of medical education. *Both stages must be developed together or the establishment of a medical school must wait until postgraduate training has been organized to the greatest extent possible.*

In any country it is of course unfortunate from the educational point of view to have to start a new medical school in the absence of clearly defined policy and adequate provision for postgraduate training in every required branch of the medical profession. If it were merely a matter of erecting a building it might be possible to ensure, even in the absence of certain knowledge as to what the upper floors were to be like, that foundations were laid sufficient to meet any later need. Medical education is not exactly like a building however. The public has to be safeguarded by ensuring adequate training in the techniques necessary for dealing with current diseases and in many countries the general license to practice is granted upon graduation or at the end of a period of internship which is no more than a final practical stage of the university course. It is true that freedom to practice, or

to have access to the facilities for practice, in special fields is often made contingent upon the completion of further training, but freedom to prescribe any of the dangerous remedies of today is still in many countries granted on no more than a university course. Thus in many countries serious limitations are imposed upon undergraduate medical education by state legislation which was designed to protect the public in a past era of medicine.

In many countries, therefore, medical schools, new and old, have as it were to lay foundations and roof at the same time. A new medical school is no more free than an old to experiment with the undergraduate curriculum under these conditions. It has the same, or even greater temptation, to fly in the face of nature and attempt to produce a complete doctor of a new kind. It is not surprising that several new schools, in both the developing and more developed countries, are concentrating upon teaching the local vocabulary of medicine (by old or new methods) at the expense of the all-important grammar. One new method, integration of teaching, makes this all too easy. It was intended to make knowledge more meaningful and its assimilation easier and quicker with the idea that the time thus saved in informing the student might be given to education concerned with principles rather than facts. If the time is not so given (which may have to be the case in schools where the integrated curriculum has used all the time of the available teachers) the result may be most unfortunate. An integrated curriculum devoid of properly supported electives and individual projects forces every student to move at the same speed on the same conveyer belt and is inevitably rigid.

Starting a new school should surely not always be thought of as an unlimited opportunity for innovation in medical education. This can only be true where the following are found together: the ability to control postgraduate training and the possibility of providing it adequately for those who are to be the general doctors (which itself requires a present supply of good general doctors as well as a nucleus of specialists), a reasonable hope of sufficient teachers for the school, a good university and adequate funds. There must also be the courage, not merely at medical school but at the national or area level, to proceed ahead of the rest of the world. Such places do exist—Newfoundland for example—but they are not numerous. Elsewhere starting a new medical school is by no means the unfettered opportunity to experiment it may at first appear—particularly because of the appalling world shortage of teachers.

In so far as there can be experiment in the undergraduate curriculum without provision or reorganization of postgraduate training (and modern licensing legislation) it can only be carried out by the staff—the faculty—and is bound to be dependent upon the degree to which they can cooperate. For many teachers the attraction of a new school is the opportunity to contribute to its planning but this is only possible if they are employed at the planning stage—a process which is costly both in money and manpower, un-

less the planning is coincidental with operating a traditional curriculum for a small number of students in temporary buildings.

The latter procedure was adopted with success by the University of the West Indies whose students took the examinations of the University of London. However, dislike of "starting small" and fear of temporary buildings becoming permanent operate against this method of beginning a new school. There are more numerous examples of a different approach—planning by a few people, the creation of a program, the construction of a building to fit it, the recruitment of staff who must accept both program and building, and finally the arrival of a class of 40 to 60 students. This method can of course be applied with either maximal or minimal "authoritarianism" and with varying degrees of detailed replanning of the curriculum but it is seldom quick (though there is the outstanding example of Kuala Lumpur). Teachers who join a new school before the first students arrive but after the planning has been completed often find the experience frustrating.

It would seem desirable that as much as possible, curriculum planning be left until those who are to execute it can share in its design. This means of course that buildings must be designed in such a way as not to restrict the choice of schedule. This is surely desirable in any case for the schedule must be expected to change frequently as the years go by, and indeed a good undergraduate curriculum must allow for the schedules of individual students to differ from each other so far as possible and necessary. Buildings must however be planned with the educational methods in mind and therefore decisions on the methods to be used in the new school must be taken early. Once taken the school will be attractive to teachers who wish to use those methods and unattractive to those who do not or cannot—who would not be desirable anyway.

Besides decisions on educational objectives and the range of educational methods to be used, other matters that must be decided before the recruitment of faculty begins include the obvious decision of geographical site. This depends on many factors and governs many factors, for it will decide the relationship of the medical school to the University, the hospital and the community. If it be true that the ideal is a school in the campus but contiguous with a hospital itself linked with a community, it is also true that such conditions will not always be available and that many quite different arrangements can be successful. Whatever the arrangement certain essential requirements must be met. The University Hospital must be adequately provided with basic medical science, behavioral science and social science: both as regards personnel and as regards space, including space for research. The intellectual atmosphere of the hospital must be that of a University without detriment to the attitudes proper to medical care of the individual and of the community. The hospital must be responsible for the care of a defined community, not so as to provide students with a full range of common diseases but to provide an adequate laboratory for the type of research (including epidemiologi-

cal) on which the future happiness of the people is most likely to depend. The hospital must be large enough to meet the needs of this community and also to take patients with clinical problems or specific needs (beyond the scope of the local medical services) from a much larger catchment area. The government of the hospital must be that of a university department which has accepted responsibility for an agreed area of medical care.

Many difficulties in achieving these requirements arise in different places. In more-developed countries there are difficulties in finding land in the appropriate area on which to build. In developing countries it is difficult to get agreement that the service load to be carried by the university hospital must be limited. Perhaps the most difficult thing to achieve everywhere is the attitude of mind of all concerned that the University Hospital (wherever it may be and whatever its physical relationship to the University) must be a University department that is responsible for the total medical care of a defined portion of the population. It must not be, as has so often been the case in the past and in some places still is, a hospital offering such facilities as it can to meet a medical school's need for clinical training. The position should be exactly the opposite—a university offering such clinical facilities as it can to the medical care of the total population while giving complete cover to one section.

At the national or regional level and at the local level there is clearly room and need for considerable compromise in uniting the demands of medical care and medical education. Similarly compromise is required in filling the needs of both undergraduate and postgraduate medical education from the total resources available. This problem of distribution is inversely proportional to the total available teachers. Where it is grossly inadequate first priority should surely, for reasons stated earlier, be given to postgraduate training. In the more-developed countries however one of the major features of post-war years has been the rapid improvement in standard of the clinical staff on what once were called non-teaching hospitals. In the United Kingdom for example there are now many district hospitals with clinicians of the highest quality.

The question thus arises as to whether the district hospitals should be used for undergraduates or postgraduates. Those who still see the function of a medical school as the production of safe general doctors are naturally committed to a policy of disseminating ever increasing numbers of its students to district hospitals for vocational training in the currently common diseases. The result of fully implementing this view would be doubly unfortunate. The important and realizable aims of undergraduate education would be sacrificed for aims which are now unattainable, and in the process it would become impossible properly to deploy the district hospital resources for the vocational training of postgraduates. Unlike students, or to a far greater extent than students, postgraduates can learn by participation in the care of the sick, and there is much vocational training that is unlikely to be acquired effectively without such participation. The re-

sources of the district hospitals are vital to that part of postgraduate training which is concerned with learning current medical practice in relation to currently common diseases.

A further part of postgraduate training for many is concerned with special techniques. As stated, some countries can offer none of this and it is conceivable that no country will forever be able to offer a complete training in every special field. The facilities for highly specialized diagnosis and treatment cannot be scattered indiscriminately across a country. Medical, educational and financial reasons all demand concentration into a limited number of places, normally where other special techniques and experience are also available and where research facilities are provided. Such concentration must obviously be based to considerable extent in University hospitals. It will dictate in large measure the contribution these must make to postgraduate training. It will not in any way conflict with, but rather will forward, their proper function as undergraduate centers.

All of these different considerations must be taken into account in deciding the site and development of a new medical school. A further consideration is that of size of the school in terms of student entry. Despite existing variations in class enrollment in the world from twelve to more than a thousand, there is little knowledge on this matter to act as a guide, and many factors have to be remembered. Important amongst them in almost every country is a serious shortage of doctors. Yet the dangers inherent in contemporary medicine are such that problems of quantity can never be given precedence over problems of quality. It would seem that one safe rule by which the size of a medical school should be governed is that its output of graduates should never be greater than that for which the country can arrange adequate postgraduate training.

It does seem very likely that the number of different disciplines that now have to be represented in a medical school, each to a degree that is professionally viable, is such that the optimum size of student entry must be greater than many have thought in the past. In the United Kingdom a figure of about 70 or 80 per annum was hitherto thought satisfactory. Now something nearer 150 seems far more appropriate. In Britain therefore the question arises as to whether it would not be better to double the size of the existing schools rather than start additional ones. A majority of the existing schools have to be rebuilt anyway because their structure is no longer adequate or appropriate. Whether or not they should be rebuilt in the same areas raises another problem. A medical school must be situated in or very close to a large population but some large centers of population are liberally supplied with doctors and others are not. Should medical schools be situated in areas of current shortage of doctors? It has commonly been held in Britain that they should on the grounds that graduates are likely to settle in the area surrounding the university they attended. It seems probable however that this view was more justified in the days when there was no postgraduate training than it is today. There is evidence to suggest that

specialist doctors are not affected by the site of their undergraduate course in choosing where they settle in practice. With major changes expected in both the training and working conditions of "general practitioners" it is hardly possible, even if desirable, to site medical schools in such a way as to be certain of providing a particular area with a more plentiful supply of doctors.

At all events it is not likely that more than a very few strictly new medical schools will be started in Britain in the near future. That country at least will have to discover whether that which is new and desirable in medical education can arise out of old schools, and it may well find this task very much easier than that which confronts those now bravely starting with a clean but empty slate.

Where a country has no medical school at all and must start one there can be no doubt that the wisest program is first to organize postgraduate vocational training, second to establish a clinical school for students and finally to add teaching in basic medical science. In this way the country obtains the maximum receipt in service to the sick in return for its efforts in medical education. It is able to offer clinical training that is designed to meet the needs of the country whereas basic medical science (which is essentially international) can temporarily be taught in other lands where there is a concentration of good quality teachers. Every country has, and needs some clinicians, who can themselves continue and augment the earlier teaching of basic medical science. Many countries do not have, and do not immediately need, teachers of basic medical science. The era has passed wherein clinicians were not scientifically-minded and science was represented in the medical school only by "pre-clinical" teachers. The tendency to begin each new medical school at the pre-clinical level is in many ways both irrational and unfortunate. It is seldom the best way to establish a strong school and it certainly does not allow the best use to be made of the woefully small number of teachers of basic medical science now available in the world.

Starting a Medical School in a Developing Country: Problems and Approaches

Edward Grzegorzewski, M.D.

A Developing Country

Expansion of education and the drive towards economic and social development throughout the as yet underdeveloped areas of the world, both in the independent countries and in those only recently acceded to independence, is probably the most significant historical event of our times. This also coincides with the growing recognition of the importance of health, and of public responsibility for its maintenance and promotion. In these circumstances, it is understandable that most of the developing countries are eager to establish medical schools as instruments for meeting the health needs of the population, and sometimes also as manifestation of national ambitions projected into the areas of education and health, if not as a symbol of a "complete national independence."

About two-thirds of all the existing medical schools in Africa and Southern Asia have been established within the last twenty years and some sixteen newly independent countries have started their first medical schools in the last few years, or are about to do so.

Although probably all countries of the world are still progressing, and none wishes to cease further development (whatever its actual stage may be), in this article "developing country" means a country (1) where there is a great discrepancy between the size of the elementary needs and the resources to satisfy them, and (2) where active efforts are made to reduce this discrepancy by increasing the resources and improving the ways of using them. These two features are possibly the greatest common denominator in the characteristics of all these countries. This also includes human resources, their development and proper utilization, and prevention of their wastage. Medical work of the country should obviously be an active and constructive part of this process, and medical education should adapt itself to this necessity. In order to focus attention on the more significant and typical aspects of the problem, the remarks which follow will mainly relate to the establishment of a first medical school in the country, although some of them could apply also to further schools.

Not infrequently one observes a tendency to think about the developing countries as a homogeneous group where the conditions are basically similar and, therefore, the problems should be approached in the same way. Of course, there are great similarities between some countries, but there are

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also essential and substantial differences; experience, vision and common sense indicate where the comparison should stop, where the situation should be understood as unique or "special" and where the "general" approach does not fit.

In addition to these particular difficulties of the developing countries, most of the problems of a new medical school in the more advanced countries exist also in the developing ones, but usually are more difficult to resolve because of scarcity of means, insufficiency and often instability of public administration, and other limitations.

The Decision

Before making the decision to start a medical school, the following questions should be answered:

First: Is the medical school necessary?

Second: What kind of school?

Third: Can it be established and maintained?

Fourth: How to proceed?

Each of these questions—though it may appear simple on the surface—covers a vast problem area and often is particularly difficult to answer in terms of conditions in a developing country. Even the first question, which may sound a rhetoric one because of the scarcity of doctors and innumerable unsatisfied health needs, requires much hard examination based not only on sentiment and good will. All implications of such a decision should be clear to those concerned, because of the proportion of national effort required. It would be excessive optimism to say that this happens in all cases when a medical school is established. The decision to start a medical school should take into account all the various aspects of national socioeconomic development, particularly the balanced advancement of health services, and the relative priorities of the various major measures aiming at the improvement of health.

Should such a thorough analysis result in a convincing favorable reply to the first question, the further questions require an equally serious study. In this connection it should not be overlooked that the role of the medical school, and particularly when it is the first one in the country, is not just to produce a certain number of doctors. Its other contributions should be equally valuable, i.e. the raising of the standard of medical care in the country, availability of a nucleus of high level specialists and consultants, research activities essential for the maintenance of scientific medicine. The establishment of a medical school is an important step towards modern civilization. Because of these valuable by-products, it would be unfair to compare the cost of a medical school with the usually cheaper per capita expense of sending medical students abroad.

Objectives and the Pattern

The second question refers to the choice of the pattern, which includes considerations about the aims of the school, the type of graduate the school

is expected to produce and the role of the school in the community and the nation. Most often, medical education was imported to the developing countries from countries with which they were in close political and cultural relationship, thus almost automatically transplanting the whole complex of concepts, traditions, terminology, habits and other characteristics developed throughout the ages in some specific historical and cultural circumstances to a developing country with a quite different past, present, and probably future.

A great deal of the cultural accretions interwoven into a system of medical education may be of value in the country where they were developed, but will become a complicating element in a foreign developing country. It is necessary to separate the elements really essential for education in medicine from those which are a reflection of foreign organizational, administrative, historical and cultural traditions and way of life; instead of these, the new school should discover and develop such structure and forms of functioning which fit into its country's system of public life, and thus render its work most effective. The medical school should not only find its proper place in the educational system of the country (which itself is sometimes just a replica of some foreign pattern), but, in many instances even more important, should become an active participant in the shaping of health services of the country. Medical education should relate to the utilization of medical manpower, both in quantitative and qualitative aspects. It should produce a graduate, not of some abstract standard, but of the quality which is particularly useful at a given period of his country's development and in the circumstances which the country can afford. One of the main distinctive features is that whereas a graduate in an advanced country is expected to adapt himself to the existing conditions of medical work, his colleague in the developing country is also expected to contribute to changing these and, in addition, various other aspects of people's lives. The common denominator of all doctors throughout the world can be briefly summarized as (1) a scientific approach to their professional work, (2) a compassionate attitude to the patient and (3) a humanitarian attitude towards the community. The content of factual information needed for the development of a scientific approach in medical work in the present rapid progress of science is a relative matter, as some of the material so painstakingly learned very soon becomes obsolete and has to be "un-learned" and replaced by more up-to-date knowledge, perhaps equally ephemeral. But what distinguishes the professional from the sub-professional worker is a desire and ability to continue self-education, which is inherent in the above-mentioned "scientific approach to his work," and these qualities should be imparted and developed in the undergraduate medical studies. This will prevent the criticism of slipping down to "feldscherism," i.e. to sub-professional level.

Another important aspect is the economy of educated manpower. At this period of ruthless race between misery and progress, indeed sometimes only for survival in a developing country, a rigorous scrutiny is needed of the

time young adults spend in learning without yet being productive. With all due respect to the intrinsic value of "pure" education at all stages which certainly contributes to the eventual raising of the cultural level, the urgency of immediate realities calls for rendering medical education more applicable to the situation. An earlier acquaintance with practical diagnostic curative and preventive measures, and acquisition of certain skills in applying them is needed in the developing countries, i.e. on the young graduate's first assignment. Instead, he may have to spend fewer years learning what may be desirable, but not really indispensable at this decisive stage of his country's development, whereas his colleagues in advanced countries often spend several years in practical training or well-supervised work after graduation. The length of fully productive professional life in tropical conditions of developing countries seems to be rather shorter than elsewhere and it is important to strike some realistic balance between the years (and monetary investment!) used for acquisition of knowledge and those of its application. Furthermore, cultural and intellectual development is acquired not only from school courses, but also from great experience of life and work.

Again, without challenging the suitability of the long "unapplied" liberal and scientific preparations for future physicians in some circumstances, one wonders why a student cannot learn about some basic biological phenomena (including the physical, chemical and mathematical aspects) in relation to human species in health and disease, but not necessarily and only in an atmosphere of pure science "non-polluted" by the heresy of its potential applicability to medicine. What amount of this scientific information is indispensable for an average student to develop scientific curiosity (through the process of learning) and ability to use this scientific alphabet for self-education, and what amount will be needed for his medical work in the near future? If the proportion could be fairly reasonably established, be it only as a compromise decision, a considerable part of the teaching time could be used for purposes of more immediate usefulness. The recent evolution in the teaching of anatomy is instructive in this connection.

It can be hoped that through proper incentives for continuous education, the medical competence of doctors after a few years of experience will not be too different, in spite of the stages through which they will go to reach that level. In the developing countries doctors will become experienced earlier in the practical handling of medical problems and will supplement their theoretical knowledge through continuous education, whereas in the more advanced countries some of the elements of these two areas may be absorbed in a different sequence. Some new developments in methodology and organization of teaching, if judiciously applied, may improve the effectiveness of the teaching and of students' learning, and efficiency in the use of time of both teachers and students. Progress in this area is particularly important for the developing countries.

The understanding of the place and role of medical work in relation to the

total health situation in the community is an indispensable element in a doctor's education. This is only seldom obtained in the medical schools of the advanced countries, partly because of the favorable socioeconomic situation including availability of medical resources and health services. In the developing countries the investment in a doctor (so much higher in proportion to average national income) will have to "pay-off" in effectiveness and productivity of "community-oriented" medical care services.

Effective utilization of the doctor's time will require relegation of some of his simpler functions to paramedical and auxiliary personnel whom he will have to guide and supervise to a much greater extent than in the advanced countries. His training should prepare him for these functions and thus make his work much more efficient.

The language of instruction is subject to many heated controversies; national cultural ambitions are weighed against the obvious advantages of using one of the more internationally used idioms. Some countries, particularly those with several different vernaculars and those where the local language is not considered sufficient for scientific instruction, choose one of the "world-wide" languages, whereas others, more uniform in linguistic structure, lean towards the national language, provided, of course, that adequate national teachers are available, which is not always the case. It seems that in many developing countries the use of a well-chosen foreign language will be not only an expediency because of scarcity of the local teachers, but an important preventive measure against professional and cultural isolation, and an indispensable medium for postgraduate studies, use of scientific publications, etc. However, the use of a foreign language should not become a means for transplanting the whole outlook of a foreign nation, and thus to continue or lead to an enslavement to one foreign pattern and ignorance of useful experiences of other cultural areas thus separated by linguistic barriers. Competitive efforts of the various assisting powers, each trying to attract the developing country to its own linguistic and possibly other spheres of influence, are not always in the best interest of the assisted country.

Feasibility

The third question implies a study of "pre-conditions" for the establishment of a medical school and of resources for its development. Obviously, such elementary conditions as availability of suitable candidates for medical studies and of basic facilities for clinical and non-clinical teaching should not be overlooked, although this is sometimes the case. The problem of the teaching staff is probably the most difficult to solve. It is a great risk to start a medical school without some realistic expectation to fill a large proportion of teaching posts with properly prepared national staff in the not too distant future.

For this purpose, the preparatory steps should include a well-planned and systematically conducted program of recruitment and training of future local instructors and eventually professors. In spite of great difficulties much

can be accomplished through such action as is shown by several encouraging examples. However, unfortunately this all-important matter does not always receive due attention, with the regrettable consequence of continuing dangerous gaps in staffing.

Financial problems are only too well-known. Even wealthy nations complain of the cost of medical education. How then can the developing nations cope with this problem? A few countries deliberately sacrifice a large proportion of their national income in order to have a medical school; this seems justified only if the school fulfills the role described above and serves the national interest.

In many countries foreign aid is instrumental in starting medical schools, and this again is fully justified and commendable, particularly if the school corresponds with the needs and conditions in the assisted country. However, the school should also foresee its continuous maintenance and make provisions for development and improvement. In some countries the whole national budget for health would be consumed by a modern medical school and its indispensable ingredients. Costly demands of medical education seem to grow faster than the national productivity.

If the solution to this dilemma cannot become evident through a rapid economic progress of the developing countries and a massive and continuous foreign aid, the alternative would be drastic reappraisal of costs of medical education and reduction to the meagre possibilities of non-affluent societies. Steps in this direction now seem unavoidable even if some uneasy compromises should be made. Here again, some examples could be found of a "frugal" and yet not unsuccessful approach to medical education and medicine in societies where frugality, not abundance and luxury, was taken as the life ideal—be it a temporary one.

There is still a strong tendency in the developing countries to imitate meticulously the foreign patterns—with all the irrelevant conceptual organizational and incidental ingredients—in the desire to maintain standards. They do not often receive the necessary encouragement and help in making a realistic adaptation of the foreign pattern to their own needs and potentialities as discussed above. Sometimes the foreign advisers find it difficult to make a rigorous examination of their own pattern's suitability and often have only limited acquaintance with other patterns. However, without a successful accomplishment of this "cathartic" process, medical education in developing countries will suffer from "mal-adjustment" and ineffectiveness in using the scant resources available to them.

In a few instances the developing countries have been able to establish medical schools by themselves, but in most cases this complex and costly undertaking needs a good deal of cooperation and assistance from abroad. Depending upon the country's resources, foreign cooperation may range from advice to the establishment of teaching facilities and provision of teaching staff.

Whereas in the past useful work was done by foreign institutions in the

developing countries without any active cooperation of the assisted country, it seems that now an institution like a medical school can properly develop only with the active participation of the relevant government and groups in the country, so that it becomes a national institution well integrated with the country it is to serve. Even if there is not yet much technical competence in the country for the running of a medical school, and much of the initial work is to be done by foreigners, the relevant groups (health authorities, educational authorities, and other institutions where appropriate) should participate at all stages of the planning, gain experience and develop a feeling of joint responsibility in all aspects of the project. The responsible country's authorities should be helped to realize the implications of their decisions, be provided with information permitting alternative organizational and teaching solutions, and should be advised on their relative advantages and disadvantages.

STRUCTURES OF MEDICAL SCHOOLS IN VARIOUS COUNTRIES

A New English Medical School at the University of Nottingham

Professor G. M. Wilson

It has often been claimed that in Britain we have produced more theoretical reports on medical education and done less to implement them than any other nation. Certainly no new medical school has been established in Great Britain since the Welsh National School of Medicine at Cardiff in 1893. The announcement by the Minister of Health in Parliament, July 27, 1964, that a new medical school was to be established within the University of Nottingham in conjunction with a new teaching hospital was thus extremely welcome. This was a particularly effective stimulus in provoking further thought about medical education in Britain as there was at last a definite assurance that something concrete would emerge. In 1964 there were no medical graduates on the academic staff of the University of Nottingham and there was clearly a need for authoritative advice on the form that the new medical school should take. An advisory committee was accordingly established under the chairmanship of Sir George Pickering, Regius Professor of Medicine in the University of Oxford. The first meeting of the committee was held in December 1964 and its report was presented to the University of Nottingham April 1965 (1). In producing their report the committee sought advice from British medical schools that had recently introduced changes in their courses and from other professional groups and individuals with special knowledge. In addition a valuable weekend conference was held at Ditchley Park with seven distinguished American medical scientists. In discharging its task the committee reviewed the defects of British medical education in the past, and outlined the purpose of a university medical school and the educational program that it would like to see in a new school. It also considered the relationship between the University and the new teaching hospital and between the new Medical Center and the community.

Defects of Past British Medical Education

All were agreed that the chief defects were overloading of the curriculum and over examination of the student. This was a relic of the time when the

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chief aim was to produce a competent general practitioner safe at the time of graduation to let loose on the public without further training. Every teacher insisted that his subject be taught in sufficient detail to ensure that this requirement was met and was satisfied only if this was demonstrated by success in an examination. Thus, the medical student passed through many entirely independent departments which arranged their courses in ignorance of what was taught elsewhere. A great burden was placed on the student to memorize material for reproduction in examinations which dominated his attitude and response to learning. In these circumstances it is not surprising that the Royal College of Physicians in 1944 reported about the end product of this system: "He tends to lack curiosity and initiative; his powers of observation are relatively undeveloped; his ability to arrange and interpret facts is poor; he lacks precision in the use of words. In short, his training, however satisfactory it may have been in the technical sense, has been unsatisfactory as an education."

Choice of Medical Students

In spite of the controversies regarding the National Health Service and the loudly expressed discontent of some doctors, this has not affected the enthusiasm of students to enter the medical profession. At no time in Britain has the competition for places in a medical faculty been keener and there will certainly be no dearth of excellent applicants to the new school. In England, medical students are chosen at about the age of eighteen. Selection should be based on intelligence as revealed by performance and examination at school, and on personal qualities and capacity for citizenship as shown by their record and by interview. While the majority of applicants will probably have studied science subjects during their last years at school, over specialization too early has serious consequences for medicine and a route of entry must be kept open for those who have concentrated on the humanities. Suitable provision must be made for them to learn the physics, chemistry and biology necessary for entry to the medical course.

The Medical Course

Most British medical schools at present have the following pattern: one year of premedical studies (physics, chemistry and biology) from which exemption may be granted if the requisite examinations have already been passed at school; five terms of preclinical studies (chiefly anatomy, physiology and biochemistry); and three years of paraclinical and clinical studies. A small proportion of selected students may spend an additional year after the preclinical period studying one of the basic medical sciences in depth for the award of an honors B.Sc. degree.

In the new school at Nottingham a change in emphasis is suggested. The medical course should consist of two periods: the first three year period, devoted to basic medical sciences, would be divided into a two year general and a one year honors course; the second, a two year period, would be devoted to clinical studies.

The first period would lead to a degree in medical biological sciences. In the first two years the general course would be concerned with those branches of knowledge within the departments of Anatomy, Physiology and Biochemistry and with general aspects of Pathology, Pharmacology, and the Behavioral Sciences. The honors year would be departmentally organized and would enable the student to study in depth a subject of his own choice; the departments providing such opportunities would include Human Morphology, Physiology, Biochemistry, Pharmacology, Pathology, Psychology, Biometry and Genetics. It is hoped that at least seventy per cent would take an honors course of this nature and that the remainder would get an ordinary degree after more general studies. The aim of this first period is to assure that the doctor of the future can appreciate and take advantage of the advances that have been made and will continue to be made in the biological sciences. The practice of medicine is becoming a scientific discipline, and every doctor should be a scientist. It is the function of a medical school to ensure that he is a good scientist. For this reason the Committee was most emphatic in its recommendation that every student should aim at studying some subject in depth for a period of one year.

Suitably qualified clinical scientists would contribute to the teaching in the first period and regular clinical demonstrations would be given, partly to bring preclinical and clinical teachers together and partly to harness the students' vocational energy. It is essential that all the teachers speak the same language and understand one another. This is most effectively achieved when they collaborate in research; to join in teaching discussions is the next most effective method.

The clinical period has as its objective to continue and develop the habit of mind acquired during the first period. Emphasis should be placed on learning by doing rather than receipt of instruction. For this reason the educational basis at this stage should be the accepted English pattern of apprenticeship founded on the clerking of patients. This should be supplemented by topic teaching and interdepartmental seminars. It is most important that during this period clinical students should feel that they are part of a team dealing with patients and should share in the responsibility for their welfare. The number of students attached to each unit in the hospitals must be kept small, not more than six, so that they all come into close contact with their teachers. Inpatient teaching, concentrated upon the problems of an individual patient, not only presents the students' work for criticism, but also provides a basis for discussion of the disease and problems arising from it including the personal and social problems of the patient. It should be emphasized again that the aim of this part of the course is not to turn out a clinician fully competent in all branches of medicine and surgery. He should learn how to approach and examine a sick patient, how to set about establishing a diagnosis, to estimate a prognosis and to assess the effects of therapy.

Intern and Preregistration Training

At present the British General Medical Council requires that after receiving the degree of bachelor of medicine and surgery a doctor must complete a preregistration (intern) year in a hospital before he can be fully registered as a medical practitioner. The proposals for the course at Nottingham included reduction of the undergraduate clinical period from the conventional three years to two years. To compensate for this loss it was suggested that the preregistration period might be extended to two years, one year to remain the standard six months as house-physician and six months as house-surgeon and the second to comprise a wide range of electives chosen for the candidate's best interests in his future work. There are two reasons for suggesting these changes. Firstly it is intended to give the student more responsibility earlier—and men and women of this age respond magnificently to responsibility. Secondly it would ensure that a doctor proposing to enter general practice received further vocational training in such subjects as psychiatry, dermatology, pediatrics and obstetrics.

It should be added that subsequent to the Committee's deliberations much more attention is being paid to the postgraduate education of the family doctor. This is the crux of the problem. If an accepted pattern of further vocational training can be agreed upon before a doctor is appointed as an independent general practitioner, the necessity for a second preregistration year would disappear. It will be some years before the first medical graduates leave the University of Nottingham and by that time the necessary decisions should have been taken. The preregistration period can then be planned accordingly.

Postgraduate Education and Research

The teaching hospital has a dual function: the advancement of medical knowledge by teaching and research, and the care of the sick. It is essential that both the physical facilities and the conditions of employment for all grades of staff are such that they have adequate opportunity and time. Nottingham is situated in an industrial area of England where there has been a considerable shortage of doctors. There will be a very heavy demand for the teaching hospital staff to provide medical services over a wide area. Arrangements must be made to ensure that this does not hinder the development of teaching and research. All the senior staff should be on a full time or "geographical full time" basis so that all their work is organized from the teaching hospital and they should not have consulting rooms elsewhere. The right for private practice would be limited to the hospital, apart from domiciliary visits. The latter have been a feature of the National Health Service since 1948 and they provide a considerable opportunity for education particularly in allowing hospital doctors and medical students to see problems as they arise in the patients' homes.

Medical Center and Community

The medical school and the teaching hospital will form the University of Nottingham Medical Centre. It is highly desirable that the Centre should not appear as something superior to and isolated from the medical practitioners around it. The teaching hospital should serve the local community; it should be the acute hospital for the appropriate area and should take a share of the accidents, the old, the chronically sick and the mentally disturbed. The Medical Centre should be concerned with the medical problems of the community.

There has recently in Britain been much discussion on the teaching of general practice in medical schools. In order to raise the academic standing of general practice it is repeatedly urged by interested bodies that there should be a university department of general practice headed by a professor in every medical school and that he should run a general practice aided by university staff to train the medical students. However, the Committee considered that proposals of this nature were too narrow; instead there should be a Department of Community Health which would be concerned with epidemiology, industrial medicine, rehabilitation, biometry and statistics and should also contain a section devoted to general practice. This section should have as part of its objective the sponsoring of experiments to improve the condition and methods of family practice. It would help generally in the organization of the health services in the area and would cooperate with general practitioners in the organization of teaching and research. Medical students should be attached for a short period to general practitioners working from health centers and they should thus be introduced to the problems of general practice as they really are. On the other hand general practitioners should be welcomed to attend regularly at the Medical Centre and to take an active part in its educational activities. In this way general practitioners would participate more in the education of the medical student than they have in the past. The Medical Centre should become the focus of the medical profession in the locality and it is essential that appropriate physical provisions be made in the new buildings.

The Development of the New School

The site for the medical school and hospital adjoins the main university campus and there is ample room both for the present scheme and for the future. The school will develop as part of the university and all should intermingle freely with those following other disciplines. By sharing in common residence, meals, sports and social facilities there will be every inducement for both medical students and staff to incorporate themselves into the general life of the University.

On the academic side a start has already been made by the appointment of a Dean, Professor A. D. M. Greenfield. He is at present Professor of Physiology in the University of London at St. Mary's Hospital Medical

School. It is hoped that a few other key appointments may be made towards the end of 1966. A planning committee has already been working on the building program and it may be possible to accept the first medical students in 1970. The pressure to produce doctors more quickly is very great. For this reason there have been suggestions that a start might be made in temporary buildings and in the old non-teaching hospitals in Nottingham. This is highly undesirable as the best available staff could not be recruited under such circumstances and clearly the excellence of the new school will depend primarily on its first staff. Furthermore, construction of the whole medical school and hospital together will enable the venture to develop with a clean slate and to make a new and valuable contribution to medical education.

SUMMARY

Some of the recommendations made by the Advisory Committee of the University of Nottingham on the development of a new medical school have been outlined. A new medical school and teaching hospital is to be built as a single unit on the University campus and will be fully integrated in the University.

The new medical school and hospital are to be designed to develop and strengthen the links between the Faculty of Medicine and the rest of the University, between the preclinical and clinical parts of the school and between the medical center and the community which it serves.

The curriculum should have as its objective the cultivation of a student whose curiosity is enhanced, who is familiar with the broad field of medical science and who has acquired the habit of learning and has assimilated the ethos of medicine.

REFERENCE

1. Report of the Medical School Advisory Committee, University of Nottingham, University Park, Nottingham, England, 1965.

Correlation between the Teaching of Medicine and Human Biology

Professeur Robert Debré

One of the many problems in all medical schools is the balance between the professional training of the physician and that of the investigator devoted to the biological study of man. The medical student faces the prospect of several careers but two seem prominent. One brings him to the bedside of the patient and one takes him to the laboratory for work in human biology. A distinct separation could be made by dividing these two apprenticeships at the beginning of training and creating 1) professional schools for future physicians, and 2) scientific schools for future biologists. We consider this an incorrect and objectionable solution. It would lead to vocational schools of medicine which would teach devices to recognize diseases and their management and would result in narrowing the horizon of each specialty. The social obligation of the physician encompasses two essential principles: 1) the human capacity to be the intimate advisor of the family and 2) the profound knowledge of man and his diseases. However, he must also possess another quality, i.e. the ability to assimilate new knowledge during his entire life time. The problems of health care change rapidly and with it the function of the physician changes.

The physician must be capable of continuing adaptation. This applies today to all professions, even the most simple ones, but it is especially true for ours. Our professional education must prepare the mind for life-long learning. Professional school should not only teach but also teach to learn. The future physician cannot learn without understanding, however. To understand, his mind must be imbued with biology because that is where progress comes from.

The relation between medicine and biology is obvious. The great discoveries which influenced our concepts and led to unexpected applications came from the basic sciences and were not made by physicians: the roles of the microbes were discovered by the chemist Pasteur; that of radium by the physicists Becquerel and the Curies; the laws of genetics through observations on nature by the monk Mendel and by Morgan, etc. The inspiration of genius comes from different directions. The community has the obligation to furnish *individual* help to those who seem to propagate original ideas. We need men who will continue in modest or conspicuous fashion the type of work which has led to the discoveries of the antibiotics, hormones, vaccines and virus. It would be of advantage if the laboratories and the research centers for these biologists would be connected with hospitals and directed by scientists who know physi-

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ology and pathology and who would remain in contact with the clinicians. Together they should design these laboratories.

The necessity of joint development creates difficult problems as to the method of study, and of curriculum but also the atmosphere, flavor, and scope of the medical school. The first difficulty is acquisition of the considerable and perpetually growing bulk of knowledge. The physician must make a diagnosis quickly, must act in an emergency, must disregard unjustified fears, choose or exclude a given therapy, and must have knowledge in many areas! Each specialty, particularly internal medicine, is multidisciplinary at present. Different disciplines do not have their own independent existences, but are interrelated. The physician of today must accept the heavy burden of acquiring knowledge. He must be a physician-biologist, as the biologist of whom we speak must be a biologist-physician.

Varieties of Training Programs. It is a task to attain this objective; it is insoluble if one strives for the absolute. As with other human problems, one has to accept compromise.

The solution varies according to place and time. Although the world has become quite small, the communities have remained quite different. Each of them has different health problems. Particularly one should not continue the error of organizing medicine in the same fashion in countries of the New World which are greatly industrialized and in the primitive agricultural regions of Africa and Asia. Each nation requires doctors of the highest quality but they must be trained for different tasks, differently practiced in different communities.

Even if we consider the countries of Western Europe and her emancipated offspring in North America, countries kindred in their economic, social and psychological structure, the differences between the nations are such that an identical plan cannot be envisioned. Medicine, more than other social functions, is linked to the whole spiritual and material heritage as well as to the way of life. The problems which it poses cannot be resolved everywhere in the same way.

However, since there is enough similarity among problems which each nation faces it is beneficial to know how each tries to solve them. We have to take particular cognizance of the manner in which America, which has taken the leadership from Europe in every respect, tries to organize its schools and to know where it has succeeded and what pitfalls in the field of medical education still exist. On the other hand, America can profit from the solutions which Europe has tried and tries today.

At this very time, every nation in Europe attempts to improve its medical training program. Reforms have been announced, rejected, studied and partially applied in Germany as well as Holland, Spain and Great Britain. In the latter a Royal Commission is at work. In France, an Interministerial Committee was established in 1956 and has been steadily working for ten years. Its principal conclusions have resulted in extensive reforms established in 1960 and now be-

ing applied. As president of this committee, we wish to offer briefly some observations.

Interministerial Committee in France. In the aftermath of World War II France found herself facing grave and urgent problems of reconstruction and reorganization. She had to simultaneously build new hospitals, restore old and archaic hospitals which had become deficient or destroyed, and adapt the university structure to the modern world.

The first task was to bring together the medical school and the hospital. As John Ellis said for Great Britain: "We need university medical centers in which school and hospital are functionally and structurally one." In this sense we have created Hospital and University Centers (C.H.U.) with a medical school, hospital and research center on the same campus, whereas until now there existed two establishments controlled by two different administrations and sometimes separated by long distances. In effect, the teaching of the preclinical sciences which we call "sciences fondamentales" given at the school have now no rapport with the hospital, the school being under the Ministry of National Education and the hospital under the Ministry of Health and municipal authorities.

An identical career has been developed for both clinicians and teachers of basic sciences which means that both groups must be employed *full time* and have *double appointments* (hospital and university) simultaneously appointed by the two ministries.

The full time clinicians must give up their private practice except for consultations twice weekly (which take place in the hospital); they have the right to a few private beds on their service and devote all of their time to their work at the university and the hospital. Moreover, under this system all persons of academic ranks in preclinical or basic sciences, from instructor to full professor, have also a hospital responsibility in keeping with the double appointment and the dual source of their salary. This responsibility consists of performing functional studies and the routine laboratory services for their respective specialties: chemistry, bacteriology, electroencephalography, electrocardiography, etc. By this arrangement both clinicians and non-clinicians have the same full time appointments, the same salary, the same working place and share the same worries.

Some professors of the preclinical sciences have accepted with pleasure participation in the activities and the life of the hospital; others have, with some good reason, maintained that the supervision of routine examinations keeps them from the pursuit of their own research. In order to lessen this inconvenience, several compromises have been made. However, it seemed vital to insist on the plan of double appointments (hospital and university) in part to avoid service examinations becoming too burdensome and, thus, to assure continuous search for improvement in techniques.

Beyond the factual requirements of the curriculum it appeared useful to the Interministerial Committee to modify the pedagogic techniques, especially to interest the future clinicians in the scientific basis underlying the facts taught

and conversely to interest the future biologist in the human application of his research.

During the initial preclinical period, it is thus necessary to organize the basic teaching in such a manner that its application to medicine is always obvious. According to the plans of the Interministerial Committee the student should receive in the middle phase of his studies (clinical phase) clinical instruction integrated and dovetailed with a progressively profound study of pathologic physiology, pathologic anatomy, pharmacology and therapeutics, and psychology (including the study of family and social problems); he should even become conversant with financial problems posed by disease. This is the reason for combined and integrated teaching of all the specialties including problems of nursing and social service. This integration is more formative for the "esprit" of our students than the individual courses of various disciplines which are still required but should be reduced.

In the final stage of study the same effort must prevail. The student should now thoroughly understand internal medicine, surgery and the specialties. At the same time the difficult task arises of putting him in contact with patients in family practice and out-patient clinics in order to teach him the practical aspect of psychology, sociology, ecology and epidemiology. In this period one has to be careful to integrate the new experiences with the basic information acquired during the preceding years so that the student remains imbued with the scientific disciplines while acquiring the humane qualities of the physician. Therefore, at the final stage of his predoctoral studies, the student must have contact with psychologists, sociologists and even economists who teach on other faculties of the university.

Thus, our acknowledged objectives are the amalgamation of the professional career of the clinician and biologist, the common life experience of the professors and students in the Hospital and University Center, and integrated teaching throughout the medical students' years.

There remains, however, the problem of having the student direct himself toward different paths according to his taste and aptitude. The greatest attention should be given now to the proper guidance of the young man facing this decision. Society is in such great need of good physicians devoted to medical care and to the prevention of disease, that it is crucial to attract the largest number of persons to this field. Therefore, the key obligation of the deans, professors and instructors is to 1) guide each student, which is not easy and 2) to organize the goal of the studies by arranging the curriculum for *each* student. To borrow a metaphor from the tailor, we may call this "made to measure" teaching.

Moreover, in the future, the practitioner will take post-graduate refresher courses in internal medicine, obstetrics, and pediatrics while the biologist will continue to be trained in the laboratories and prepared for research.

According to this plan the school will organize a special curriculum for the development of researchers and teachers in the basic sciences through work in the laboratory and subsequently will award degrees of "master of human

biology" or "doctor of human biology" which will, in the field of laboratories, correspond with the titles of "residents" and "assistants" in clinical medicine. It is planned that masters and doctors in human biology will share with the personnel of the Faculty of Sciences in the management of the Research Centers built on the hospital-university campus. These will report to the Ministry of Scientific Research or to the "Education Nationale" (Centre National de la Recherche Scientifique), or to the "Santé Publique" (Institut National de la Santé et de la Recherche Médicale), or to private institutions (Association Claude Bernard, etc).

These are the plans of the French reform, partly under way, with regard to the full time and double appointment scheme, the affiliation of the hospital and school, and, in experimental stage, the changes in teaching appointment and curriculum.

Design of the University for Medical and Natural Sciences, Ulm, Germany

L. Heilmeyer, M.D.

The architects of a new medical school with responsibility for research and teaching must take into account developments of medical science in the next decade. In this paper such developments which can already be discerned today are described.

In the future, much more even than in the past, basic research in the natural sciences is going to determine the face of medical science. Therefore, successful medical research will be possible only through broad participation of natural scientists. These basic sciences will also have to be more strongly represented in teaching than they were until now. The imbalance in favor of morphological observation, as it is particularly in Germany, must be replaced by stronger emphasis on physiology and biochemistry. But aside from the natural sciences, the outlook of modern medicine will be influenced in the future by stronger representation of the psychological sciences. New knowledge in the fields of depth psychology, the behavioral sciences, and of sociology will have to be more fully represented in medical teaching and medical research. Another challenge concerns the solution of immediate problems of medicine which are dependent on the future developments in technology, and on the increasing complexity of civilization. Therefore, in a modern medical school the problems of preventive medicine, social medicine, occupational medicine, rehabilitation, geriatrics, air travel and of space medicine should have greater emphasis.

Another important factor in planning a new medical school, is the tremendous expansion of our knowledge which necessitates a much larger number of teachers and much closer cooperation between teacher and student. Only in a community of researchers and teachers can diverse specialized knowledge be built into a meaningful unity. One prerequisite in reaching this goal is the elimination of rigid borders between departments and between faculties. This goal will be obtained by bringing into close and permanent contact the representatives of the natural sciences, of the basic psychological sciences and the other basic sciences with the representatives of theoretical and clinical medicine.

To achieve this end the plans for the University of Ulm include, therefore, a new approach: besides three *faculties* (one of natural sciences, one of theoretical medicine and one of clinical medicine), six *specialist groups* are being organized. These groups, devoted to a specific area, are to bring in

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contact, in a special institution of the university independent of faculty borders, the basic scientist and the physician with theoretical and with clinical interests. Moreover, a center for basic clinical research will be created with numerous research laboratories where natural scientists as well as theoretically and clinically oriented physicians will engage in combined research. Furthermore, *ad hoc research councils* will be set up, transcending the boundaries of specialist groups and faculties, to plan broader common research projects and facilitate their execution.

The specialist groups represent essentially the organizational framework of the scientific life of the university. They are to arrange scientific cooperation in their respective fields. They evaluate the theses which form the basis of granting doctorate degrees and teaching privileges in the faculties. In this respect the faculty has mainly an executive function; also major academic appointments are initially prepared by these groups, and the students participate in the scientific life of the specialist groups through work in their seminars. Plans have been made for six specialist groups at the University of Ulm. Table 1 illustrates the relation of the four inter-faculty specialist groups to the three faculties.

Specialist Groups

The specialist group in physics unites the basic physicist with the researchers of applied preclinical and clinical physics.

The specialist group in chemistry combines in the same manner the chemists with the biochemists and the representatives of clinical-chemical research.

The same is true for biology which combines biologic basic sciences with the corresponding specialties of medicine in a morphologic and physiologic division.

The specialist group in psychology leads from general psychology and behavioral science in animals (zoology) via sociology and anthropology to the clinical areas of psychosomatic medicine, psychotherapy, psychopathology and psychiatry.

Aside from these four specialist groups which involve all faculties, two more clinical specialist groups are being established to deal with surgical and non-surgical clinical medicine.

Each specialist group consists of the chairmen of the respective departments, of the division chiefs and of an adequate representation of the other persons of professorial rank. A chairman or division chief may belong to several specialist groups, however, he has a vote only in one group. The specialist group elects a group chairman and a deputy chairman for a period of three years. The entire teaching staff and all students concerned with the area of the respective specialist group participate in the group seminars.

The creation of specialist groups permits inclusion of the natural scientists working in the various theoretical and clinical departments in an organi-

TABLE I

Organization of School

Specialist Group	Specialist Group	Specialist Group	Specialist Group
Physics	Chemistry	Biology	Psychology
Faculty of Natural Sciences			
Experimental Physics	Atomic Physics	Chemistry	General Psychology
		Inorganic Chemistry	
		Physical Chemistry	
		Organic Chemistry	
		Botany	
		Physiol. Sect.	
		Zoology	
		Morphol. Sect.	
		General Microbiology	Behavior Research
Theoretical Medical Faculty			
Biophysics	Radiation Biology	Human Physiology	Medical Psychology with Depth Psychology
		Anatomy	
		Histology	
		Cytology	
Clinical Faculty			
Physical Therapy	Diagnostic X-ray & Therapy	Pharmacology	Psychotherapy
		Patrol. Pathol.	Psychosomatic Medicine
Climatology	Nuclear Medicine	Bacteriology	Psychopathology
		Virology	

zation of the university. This provides for their further career and employment depending on merit, which was until now impossible because of the separation of the natural sciences from the medical faculty. Consequently, second echelon scientists often worked in a theoretical medical or a clinical department of the medical faculty where they found themselves at a dead end and without possibility for advancement.

Clinical Research Center

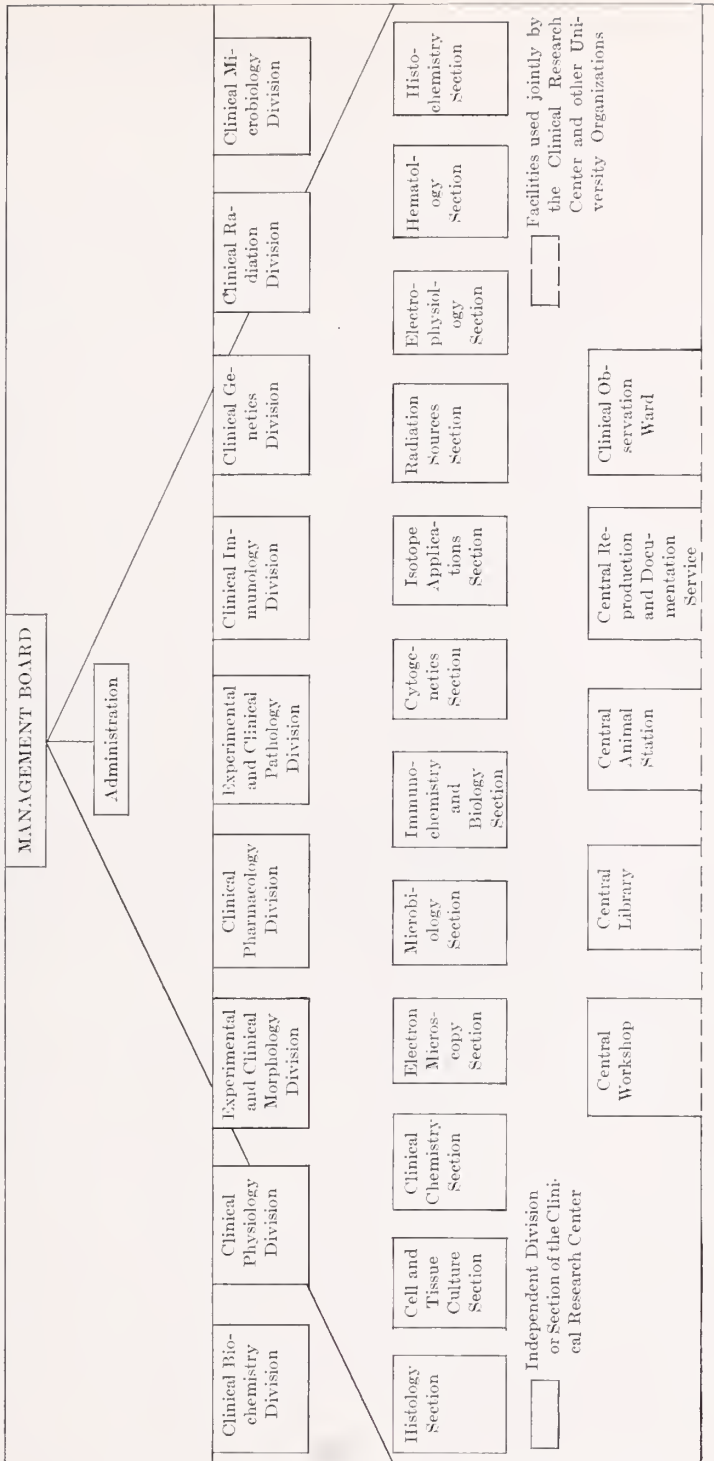
The Center of Basic Clinical Research shall be the scientific force of the university. It should stimulate the further development of medical science. The clinical research center should create an environment for scientists of various fields to cooperate on research problems posed by clinical medicine. It should provide working space for young clinicians to adequately investigate special research problems. They can obtain expert advice here too and should have specialized technical assistance, provided by a *service section*, to solve methodologically difficult problems. The clinical research center should serve particularly as a link between theoretical and clinical medicine on one hand, and the natural basic sciences on the other. Under this arrangement newest scientific discoveries can be utilized by medicine without delay. The greatest possible proximity of a research center and a clinical department must be reflected in the architectural planning. Thus the scientist at the bedside may cooperate in a productive way with researchers in the laboratory. Clinical medicine will be stimulated by scientific ideas and, in turn, theoretical medicine by clinical observation. The plan calls for nine departments in the clinical research center (Table 2).

The heads of the departments are as a rule full professors who are qualified by their research in areas related to basic science or clinical medicine. They are primarily representatives of theoretical or clinical medicine who now dedicate themselves exclusively to problems of clinical research. This seems especially important since the conventional basic science university departments usually do not have the time and possibility to devote themselves to clinical problems. They are mainly concerned with their tasks in basic research and preclinical teaching. In addition, facilities should be created to accommodate new aspects of clinical science as independent divisions in the research center.

Aside from the departments there will be so-called *service sections* which have the necessary techniques and equipment for effective research throughout the entire center. These laboratories will be supervised by either academic or technical personnel of the university. One part of the sections will perform mainly routine procedures in histology, clinical chemistry, hematology, etc. In other sections procedures will be performed which are still in stage of development, such as electron microscopy, cytophotometry, histochemistry, etc.

The administration of the research center can be either in the hands of one single director or of an elected triumvirate. One director will be appointed if a person with special qualities is available; for instance, he should have the

TABLE 2
Center for Basic Clinical Research



ability to induce leading scientists to talk to each other and to create an active exchange of experiences between scientists in the center and the members of the department within and outside of the university. A lay administrator will ease the administrative burden of the center.

The Research Council

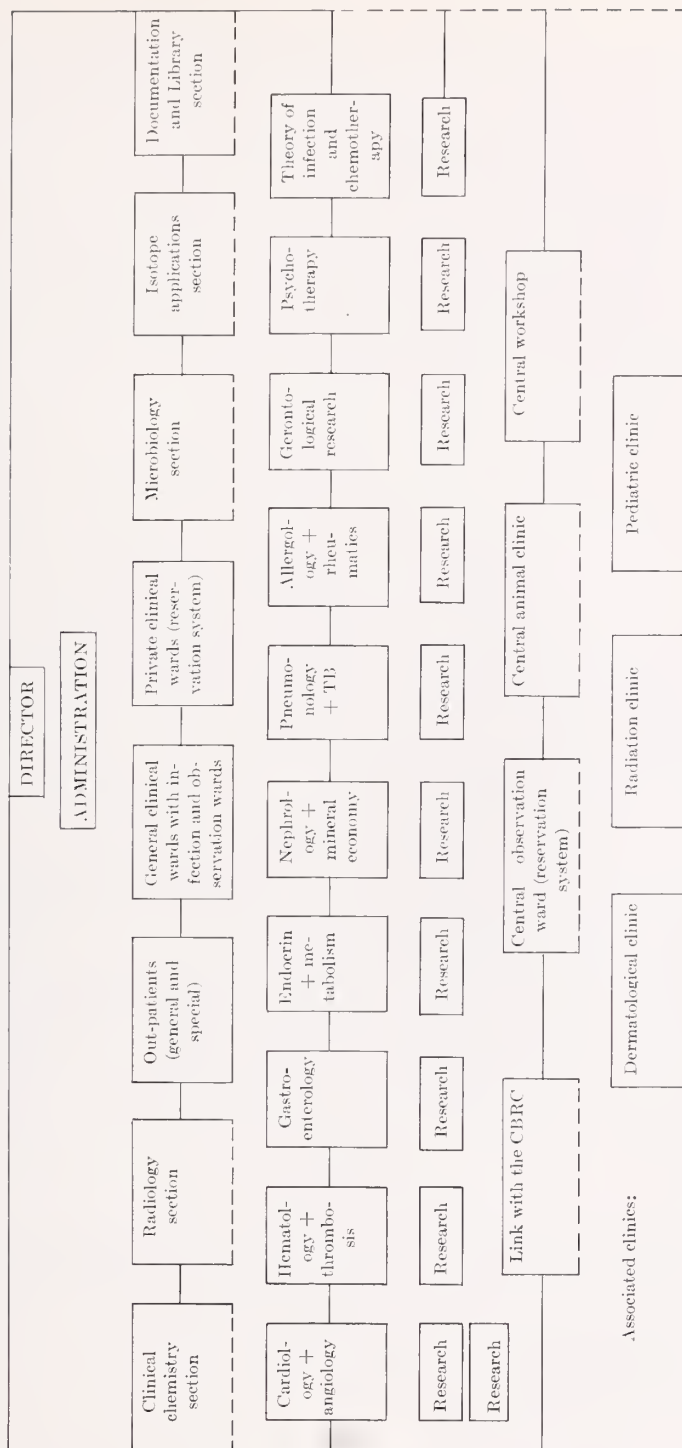
This is not a permanent organization of the university. It will meet in answer to specific demands. It consists of the heads of the specialty groups and of a chairman elected by them. Depending on the research problem in question, additional experts may be called in. The research council is to make proposals for the plans and execution of research problems, which transcend the specialist groups. If the feasibility of a problem has been decided upon, the council will make recommendations as to the necessary personnel and equipment and will assist in their implementation. More encompassing projects to be executed under the supervision of the council should deal particularly with preventive medicine and also with occupational and community medicine. It would be better to deal with them through such inter-faculty bodies than through a single department created for this purpose. The range of research possibilities would thus be facilitated because of the broad nature of fields represented on the council.

While the main research responsibility in the university lies with the specialist groups and the Clinical Research Center, the main function of the faculty consists of the organization of the teaching program, of the examinations and of the academic administration. The president (rector) of the university will be elected on a permanent basis contrary to current custom in Germany. His activities will be full time. He can be removed on recommendation of the senate. The executive administrator of the university reports to the president. The president (rector) has available as advising groups, the large senate (which consists of all full professors) and the small senate which represents an elected executive committee of the large senate.

The Disciplines

An important problem for the present and future is synthesis versus specialization in medicine. Extensive specialization is urgently needed for medical research and for specific demands of patient care. By contrast, the patient who has ailments involving several organs requires integrated medical thinking. For this reason the large units, like internal medicine or surgery or neurology, cannot be abandoned. Rather, a wide framework should be created which should encompass the different subspecialties. Internal medicine serves as an example (Table 3). The subspecialties do not have their own beds except under special circumstances, e.g. infectious disease unit, intensive care unit, etc. The heads of departments have their own routine and research laboratories and act as consultants for the entire Center of Internal Medicine. They take responsibility for the care of patients with diseases relevant to their specialty and act as consultants.

TABLE 3
Center of Internal Medicine



At the head of the center of medicine or surgery is a chairman who is responsible for the organization of medical care, for regular conferences and the teaching program in his particular field. The department heads serve in rotation for three or six months of the year as attending physicians on the general wards. This will counteract the limitations in the general medical knowledge which threatens every specialist.

A characteristic of the plan of Ulm also consists of the establishment of close connections between the university departments and medical practitioners in the town. A number of resident physicians together with students will be employed to substitute for the physicians with outside town practice so that they in turn can spend time at the university department. A new relationship between university and physicians in practice will thus be developed through cross fertilization. The structure of the theoretical centers, too, should undergo a similar change. In one center there will exist several chairs of related disciplines or several departments will be combined into one larger unit, such as a center. Thus expensive apparatus and specialized manpower will be utilized cooperatively for the common good and research results of different departments can be evaluated together. It is the special principle of the medical and natural science University for medical and natural sciences of Ulm to make equipment and departments available to clinical research. These were conventionally utilized only for basic research. Moreover, the principle of integration of clinical and theoretical medicine with basic science will be strengthened by the specific structure of the theoretical and clinical departments.

Other important links in the university are the central installations which include:

1. Central library to be organized according to the principle of 'centralized decentralization,' which means central accession and cataloguing of all periodicals and books, however with decentralized storage of the material which is essential for the different working areas.

2. Record and computer center in close connection with the library.

3. Central animal institute with all facilities for animal procurement, supervision of animal experiments, animal surgery and diagnostic facilities in the broadest sense. This institute is under the direction of a veterinarian.

4. Medical illustration center where all drawings, tables, photographs and films will be produced for research and teaching. It should also provide copying facilities. Experts should be employed to assist in editing of research reports.

5. Central workshops, under the direction of a graduate engineer, divided into different sections such as carpentry, glass blowing, mechanical instrumentation and *electronics*. Special emphasis shall be given to the section of electronics because of its importance in modern medicine.

6. Central pharmacy.

7. Central supply.

8. Central Blood Bank where routine functions and research on blood fractionation will be carried out.

9. Guest and conference house. It was possible through donations to purchase a medieval castle of the 14th century with a belfry, 13 miles from Ulm, 15 minutes on the Autobahn. The castle, "Schloss Reinsburg," is situated on a hill above the Danube surrounded by forests with a beautiful view of the Bavarian Württemberg countryside. It will have quarters for visiting professors and other guests of the university as well as club and conference rooms ("International Institute for Scientific Cooperation"). Initially it will also house an institute for preventive and social medicine. This secluded retreat in the countryside should encourage scientific interchange. Here seminars of specialist groups and other interdisciplinary conferences can be held.

Academic Chairs

Only those chairs will be mentioned here, which do not exist at all other schools.

The natural science faculty is to have 16 chairs: besides the conventional ones in physics and chemistry; 2-mathematics, 2-biology, 1-molecular biology, 1-behavioral sciences, 1-cybernetics, 1-experimental psychology.

The theoretical-medical faculty consists of 22 chairs; among them 1-biostatistics and research design, 1-human genetics, 1-evolutionary physiology, 1-clinical psychology, 1-medical sociology and 1-virology and immunology.

The clinical faculty has besides the traditional chairs: 1-psychosomatic medicine, 1-psychotherapy and 1-clinical pharmacology, and in addition 22 other full professors. Internal medicine and surgery will have five chairs each for different subspecialties and also additional full professorships as section chiefs.

As a special characteristic of the University of Ulm three undesignated chairs are planned for the humanities or other sciences which should be given the opportunity to develop areas of their discipline relevant to medicine. Thus it is an intriguing idea to create one chair for philosophy of medicine and science, one chair for medicine and law and one chair for theology and medicine. There will be five free chairs for visiting professors which will permit distinguished foreign scholars to work for a prolonged period of time at the new school.

Teaching Program

The University of Ulm should have about 800 medical students, 140 each year, and about 700 graduate students in such sciences as physics, mathematics, chemistry, biology and biochemistry. Two curricula will exist for the medical student.

One involves complete training for the practicing physician and consists of 12 semesters, corresponding to six years. It is considered important to

provide good training in the natural sciences and also instruction in psychology, sociology and psychological anthropology in the preclinical years as well as in psychosomatic medicine and psychotherapy in the clinical years.

Furthermore, Ulm has planned a second curriculum for students who want to become pure scientists in theoretical medical institutions. The curriculum is the same for all medical students until the eighth semester, then they part. The training for practicing physicians takes place mainly in the teaching hospital. The training for a career in sciences basic to medicine is given in the respective theoretical medical departments. The study concludes after 11 semesters with a degree in biology, biochemistry, biophysics, pathology or pharmacology. This training is to introduce the student in his young creative years to scientific research.

The Ulm plan tries new methods in research and training. The prerequisite for success is a dedication to extensive cooperation by the scientists and teachers.

I would like to close with the opinion of E. P. Cronkite of Brookhaven about the "Report of Ulm":

The central theme of the proposal appears to state that the new school will retain the proved valuable aspects of classical German medical education and will introduce those facets of American, British and other foreign systems that have developed since about 1920 and have proved to be of use in producing well rounded, humanistic, technically trained physicians familiar with the practical and fundamental aspects of the art and science of the clinic and the laboratory. The proposal does not stop with incorporation of the proved features of other systems of foreign countries but introduces new ideas and concepts. These avant garde ideas may very well constitute the next progressive step in medical education which could well be in part adopted as a pattern for future new medical schools outside of Germany. If so, this could be the mid-twentieth century contribution of Germany to medical education and research. If this were to materialize this would be a fitting recognition of the contributions of the nineteenth century Humboldt tradition in medical education.

The Organization of a Medical School

Joseph Stokes III, M.D.

Medical schools are rarely held up as examples of good organization. Quite the opposite is true. They have recently come under criticism for their inefficiency, since any such bungling adds to the cost of medical education and medical care which society believes is already too high.

This inefficiency stems from many roots. By tradition medicine carries with it a heritage which dictates that each individual physician should be able to manage by himself any problem presented by any patient so long as he is given sufficient resources and freedom of action. There is reason to doubt that this dictum has ever been true, and it has certainly been an untenable assumption in the urban areas of this country for the last 60 years. The healthiest part of this heritage clearly identifies one physician as responsible for one patient, and it views with alarm anything, including excessive organization, that threatens to diffuse that responsibility.

The most rational reason for loose organization within a medical school concerns the variety of purposes that it must serve. A medical school should foster the pursuit of new knowledge in the life sciences and other related fields of scholarship and then facilitate the transmission of that knowledge from one generation of physicians and medical scientists to the next. It should also bear a unique responsibility to develop new systems of medical care which can then be translated into health services and facilities outside of the university medical center.

Table 1 illustrates the interrelations of these three major functions of a medical school, and it illustrates the relative responsibility that each of the different organizational units within a medical school should assume for each function. Even though this table assumes that the school as a whole bears more responsibility for the teaching of medical students than it does for either patient care or research, the prime responsibility for each function still rests with the individual faculty member. Despite the recent trend toward "team approach" to research, teaching, and patient care, of which interdisciplinary teaching is a good example, the principal *raison d'être* of a medical school should be to provide faculty and students with the necessary services and facilities with which they can carry out the functions of the school whether they work alone or in cooperation with others. The system should be designed not to exploit but to serve the individual. This is in sharp contrast to many other organizations with very different objectives. An

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army or a highly competitive business organization must concentrate its power and decision-making in order to effectively wage war or make profits.

Wise organization dictates that a medical school should be divided into various units. Only through such organization can sufficient institutional stability be developed. For example, a modern medical school may be subdivided into between 8 and 30 departments which, in turn, may be made up of two or more divisions. Large departments such as medicine may have as many as 12 to 15 divisions such as cardiology, infectious disease, and rheumatology. The size and complexity of each department may vary greatly from small departments such as preventive medicine with 6 to 7 faculty members to large departments with 60 to 70 full time faculty. Each unit in the organization is tied together by certain common features of training and experience and a need to join together in order to reach certain common objectives—be it a research project, a course in the curriculum, or a problem of patient care. However, the strongest and most stable cohesive force binding

TABLE 1
Functional Organization of a Medical School

Organizational unit	Research	Teaching	Patient care
School	+	++	+
Department	+	++	+
Division	++	++	++
Individual faculty member	++++	+++	++++

+ = minimal responsibility; ++ = slight responsibility; +++ = moderate responsibility; ++++ = prime responsibility.

such units is a set of principles to which each member of the unit subscribes and which enables all members of the unit to work effectively together in all phases of their activities. Thus a division such as cardiology may be made up of 3 to 10 faculty members each of whom have shared certain training in medicine and heart disease and who share certain common facilities such as a cardiac catheterization laboratory. Yet each member also has some knowledge, skill, or attitude which is not shared by the others and which is unique. Such unique assets should be more than tolerated, they should be encouraged and the organizational system should provide each faculty member with enough freedom to develop and practice these special skills and to pursue a research project on his own. There are critical limits to the effective size of such units. A division with less than three full time faculty members is too small to provide continuity in teaching and patient care while a unit of more than 20 becomes too large and unwieldy to maintain effective communication.

Somewhat the same problem affects the effective size of the policy committee of the school. If the number of represented departments exceeds 25, the size of the policy-making group becomes too large for effective, concerted

action. It is for this reason that large, multifaceted departments are to be preferred to many small ones. Small departments are weak, yield to external pressures, and find it difficult to develop the resources to carry out varied academic demands. They also tend to be built around single scholars so that they may serve only the special interest and abilities of one individual. They may also become narrowly oriented in a direction away from the central concern of their discipline. On the other hand, large departments with many semiautonomous divisions usually prove to be more flexible and provide a more effective means of communication. In a department of surgery which includes anesthesiology and ophthalmology, the binding principles may be quite general (e.g. the operating room procedures). Yet, if sufficient autonomy is given to these units such an organization is far preferable to one which creates separate departments of each of its subspecialties.

The principal defect of large departments is that it places a heavy administrative responsibility on the department chairmen, many of whom have now become as busy as were deans 20 years ago. Few medical school department chairmen (or deans for that matter) have ever had any formal training in administration and, therefore, have no choice but to learn by means of the painful process of trial and error. Since they may be understandably insecure in their abilities to grapple with administrative problems, they may be unwilling to delegate their academic responsibilities effectively to division chiefs or their administrative responsibilities to nonacademic personnel. The medical school administration must also recognize the need to provide each department with resources that are adequate to manage the administration. Such individuals as business managers, laboratory business officers, and other administrative assistants are becoming increasingly common as the size and complexity of medical schools increase. It is also important to weigh administrative ability and experience in choosing department chairmen particularly of large departments. Too often faculty promotions reflect only research and teaching accomplishments, and a successful medical scholar may find himself as chairman of a department where most of his energies will be directed to administration. Such chairmen will be frustrated if they are inept at administration and are unable to carry on with their research and teaching because of administrative demands. Department chairmen must be able to gain real satisfaction from helping to develop younger and less experienced members of their departments. They must also be aware of the critical need to develop and maintain effective communication between the various units for which they are responsible and to involve each division chief in the decision-making process in their departments. At the same time, they should delegate sufficient authority and responsibility to their subordinates in order to permit sufficient freedom of action.

In any medical school, but most particularly in those new schools where rapid growth can be expected, organization should be determined to a large extent by ability to respond to change. Biomedical knowledge is expanding logarithmically and all medical school organization must recognize this hard

reality. Superficially one would think that small departments would be more flexible than large ones. However, the opposite is usually true. The most effective change takes place through orderly growth with the addition of new units, expansion of active units, and attrition and consolidation of inactive, outmoded functions. In large departments such a process can take place relatively unobtrusively without markedly altering the overall complexion of the department too rapidly.

It is well recognized that tenure provides senior faculty members with a kind of security which is essential to good scholarship. However, so critical is the leadership role of the department chairman that a tenure commitment to this position for a vigorous young chairman in his middle forties will mean 20 or more years in one office. This will almost certainly result in conservative influences and rigidity of program. On the other hand, planned rotation of the chairmanship after a set period of tenure of three to five years will limit the commitment of the chairman and weaken his authority particularly during the later phase of his term of office. For both of these reasons, tenure of the chairmanship should be indefinite, but with provision for regular review every three to five years. Such a system provides a balance between the two extremes. It encourages the continued tenure of an effective chairman while allowing a systematic mechanism for removal of an ineffective individual.

Basic science departments deserve special consideration since they differ from other departments of the school in not having any direct patient care responsibilities. They were developed in most medical schools after the recommendations of the Flexner Report (1) for the purpose of linking the applied problems of medical care to the general body of knowledge within the parent university. Since such disciplines as anatomy, microbiology, and pharmacology are relatively narrow they are rarely responsible for more than one course over one or two semesters in the curriculum. As a result they have had difficulty in responding to changing circumstances since their conception. The research programs of many of these departments are virtually indistinguishable and have tended to drift to a basic level. Therefore, the modern department of biochemistry in most medical schools is virtually indistinguishable from its counterpart in the graduate school of the same university. Indeed, so similar have such departments become that many have developed joint training programs for graduate students. At the same time, they have become increasingly removed from the special teaching needs of the medical student.

As a consequence, in planning for the University of California, San Diego, School of Medicine we have elected to divide the traditional training responsibilities of the medical school basic science departments between the graduate departments such as biology, chemistry, and psychology on the one hand and the clinical departments on the other. Under such an arrangement the graduate departments will teach most of the first year medical

school curriculum and the clinical departments will be responsible for the teaching of organ structure and function beginning in the second year—a year earlier than the traditional beginning of their teaching responsibilities. The clinical departments will also give such courses as pharmacology, pathogenic microbiology, and an integrated course in the neurosciences. Such a departmental structure should have the added advantage of bringing the clinical departments functionally closer to the heart of the University to match the physical integration of our facilities.

The increased size and complexity of programs within medical schools today has led to a tendency to assign the different functions of research, teaching, and patient care to separate faculty members. Many medical schools weigh creative research most heavily in promoting faculty and discount teaching and patient care. As a result, there has been a trend toward limiting the teaching responsibilities of investigators and giving these teaching “chores” to less creative members of the faculty. Such a trend should be viewed with alarm. Recognizing the fact that each school needs, and will attract, faculty with an infinite variety of abilities, each school should permit a complete spectrum of activities for each faculty member. If too large a gap develops between research and teaching, both functions will suffer. The stimulus to the investigator of young and uncommitted minds is vital to his work, and teaching will lose its freshness if it is long isolated from creative research. Whitehead (2) put this most effectively when he said:

Imagination is a contagious disease. It cannot be measured by the yard, or weighed by the pound, and then delivered to the students by members of the faculty. It can only be communicated by a faculty whose members themselves wear their learning with imagination. Do you want your teachers to be imaginative? Then encourage them to research. Do you want your researchers to be imaginative? Then bring them into intellectual sympathy with the young at the most eager, imaginative period of life, when intellects are just entering upon their mature discipline. Make your researchers explain themselves to active minds, plastic and with the world before them; make your young students crown their period of intellectual acquisition by some contact with minds gifted with education. There must always be a certain freshness in the knowledge dealt with. It must either be new in itself or it must be invested with some novelty or application to the new world of new times. Knowledge does not keep any better than fish. You may be dealing with knowledge of the old species, with some old truth; but somehow or other it must come to the students, as it were, just drawn out of the sea and with the freshness of its immediate importance.

The expansion of the health sciences since World War II has led to the need for increased coordination between all professional schools involved in health training. Many universities operate schools of dentistry and nursing in addition to their school of medicine. In addition, there are teaching hospitals which are either run by or affiliated with the university, to say nothing of schools of public health, social work, veterinary medicine, pharmacy, and medical technology.

The most common mechanism used to coordinate such activities is to

develop a coordinating council of the chief administrative officers of each school under the chairmanship of a vice president for health affairs. In communities where most of these schools are affiliated with different institutions a community coordinating committee can serve the same purpose. Most of these professions and disciplines had origins in the applied aspect of their fields and only recently have they joined ranks with academic institutions. As a result, it has been difficult to effect optimum cooperation between the various health disciplines. The physician's role as the leader of the health team has not been emphasized sufficiently in the training of physicians nor is it accepted by other members of the health professions. The attempt by nursing to gain increased prestige and professional recognition through emphasis of teaching and administration has created unnecessary jurisdictional friction between nursing and medicine. At the same time, the shortage of nurses and other paramedical trainees is far more acute than the current shortage of physicians. In recognition of this fact, medical schools and physicians should accept a more extensive leadership role and develop more effective communication between medicine and the other health professions than has been provided in the past.

Finally, in considering the organization of a medical school it is important to recognize the principal means by which society influences its academic programs. The formal mechanism for such control is through the governing bodies of the university. Thus, in a public university the executive and legislative branches of state government can primarily influence, through budgetary means, the complexion of a school although this direct effect should be mediated through the Board of Trustees and the President's office. In a private school the trustees are not under direct governmental control, but must play an even more active role in establishing general policies of the school.

The second strong influence on medical school policy comes through direct extramural support of academic programs from the federal government and from private foundations. The latter, in particular, have had a highly progressive influence on medical school programs since they can be deliberately experimental in their support of new and unique programs. However, the federal government's role is now so large that its influence is profound in all phases of research, teaching, and patient care.

Finally, the most effective and direct influence on medical school programs comes from within the school itself. Despite the obvious influence from external sources, it is still the individual needs and wishes of the faculty, the students, and the patients which shape the programs of any medical school. Similarity in programs from school to school is evidence of this fact since faculty, student, and patient needs are much the same from one school to the next. It is for this reason that medical schools should largely look to themselves in seeking an organizational pattern that will meet their own

special needs rather than designing programs to meet medicine's needs in general.

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New Medical Education in the Old Southwest

Reginald H. Fitz,* M.D. and Robert S. Stone,† M.D.

The decision to establish a School of Medicine at the University of New Mexico in Albuquerque, New Mexico, was reached by the Regents of the University in 1960 and was approved by the State Legislature at its 1961 Biennial Session. This decision culminated 15 years of conjecture by a few imaginative individuals and a year and a half of intensive study initiated by the administration of the University. The W. K. Kellogg Foundation recognized the potential importance of this addition to the scope of the University activities and awarded a substantial grant in 1960 for the development of the School. The Dean was selected and appointed in 1961 with the immediate assignment to establish a functioning school of the basic medical sciences which would, at an undetermined time, become a four year, degree awarding School of Medicine. Beyond this primary assignment and responsibility, and the implicit necessity that the School meet accreditation standards and adhere to the academic, administrative and fiscal regulations governing University operations, there were no restrictions.

That the Medical School was to be located on the University campus and that the University administration had a strong and long-standing commitment to the principles of academic freedom were conducive to effective recruiting. That the University was located in the middle of metropolitan Albuquerque and had approximately 180 on-campus acres available for the ultimate development of a Medical Center also augured well.

Early developments included planning and financing a basic medical sciences building, the establishment of a Library of the Medical Sciences, and the creation of interim teaching and research space in remodeled existing structures or removable new one story steel "temporary" buildings. Available clinical facilities included a 204 bed general hospital adjacent to the site of the Medical School and a 500 bed "Dean's Committee" Veteran's Administration Hospital three miles distant. An agreement was reached with the former whereby the School assumed responsibility for the direction of the professional, educational and research programs at the hospital.

The first entering class of 24 students was enrolled in Fall 1964. Inasmuch as the decision was reached in 1966 that the School should move without interruption to the full four year program, it is expected that the members of this class will receive the M.D. degree in 1968.

It is the purpose of this essay to describe the nature of the educational pro-

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gram that has evolved. Before proceeding to a detailed description, however, it is appropriate to emphasize a number of premises and principles assumed by the Dean at the time of his arrival, for adherence to these played a significant role in the establishment of the faculty template and subsequent program development.

Firstly, it was presumed that the environment in which medical education takes place must be alive and stimulating from the standpoint of scholarship and scholarly productivity, including research, and that research should not be dissociated from education. If the trend to broaden the base for scientific research by cutting across conventional disciplinary lines were essential to research, it should be accompanied by a similar movement in education. Within the setting of medical education, if interdisciplinary research were to be furthered, then the base for medical education should be interdisciplinary as well. One principle was considered fundamental to the development of an interdisciplinary curriculum—namely that no department would be permitted proprietary interest in curricular time. Adoption of this principle by an established school with a conventional program appears to require a true revolution. Great credit must be given to the Western Reserve University School of Medicine for its leadership in recognizing and taking this essential step in the early 1950's. In considering the development of the University of New Mexico School of Medicine program, it was assumed that if this step were taken as a *firm fait accompli*, future curriculum development would remain flexible and modifications would be evolutionary. Commitment to this principle had an interesting effect on recruiting activities, for although several prospective candidates excluded themselves from consideration on this basis alone, it proved a primary attraction for others.

Serious consideration was given to the possibility that one might establish a faculty without the usual departmental structure. This possibility was deferred on the basis that it might prove too hazardous a distraction in recruiting a faculty with the best possible qualifications. Moreover, irrespective of labels, it would be necessary to establish leadership in various areas of research and education. Accordingly it was decided that the conventional departmental names would be used. It would avoid confusion, and moreover was not irrevocable.

Another major assumption made at outset was that the primary goal of medical education for most students is to become a physician. This goal should be in clear view throughout the entire medical education program.

Finally, although it was deemed appropriate for the Dean of a developing medical school to enunciate certain general principles involving curriculum and program development, the prime responsibility for detailed planning and program implementation must reside in the faculty who conducts the program. The program must remain flexible so that each new member of the faculty has an opportunity for the effective expression of his own views concerning medical education.

The basic design of the curriculum utilizes two major components which function concomitantly in each of the first three years. These are entitled

Medical Biology I, II, III and Clinical Science or "Medicine" I, II, III respectively.

The fourth year is planned as an elective year with each student selecting his own program from among several sets of electives, at least one of which will be primarily clinical.

The two major components, the one essentially basic science and the other directly patient-oriented, are related temporally and in content. However, in reviewing the total program it is convenient to discuss the two consecutively.

Medical Biology comprises a unified and interdisciplinary study of principles usually subsumed in the traditional basic science disciplines augmented by what might be termed clinical physiology and clinical biochemistry. During the first year the dominant theme is the normal state, the second year the disease state, the third year "illness" (i.e. the expression of disease in a particular human being).

A more detailed analysis of the program components follows. In Medical Biology I, the initial eight weeks are conceived as an introduction to molecular, cellular and tissue biology at successively increasing levels of complexity. In this sequence, following a brief review of some aspects of physical chemistry, biochemical principles are presented with proteins—their composition, structure, formation, activity and metabolism—as the reference points. This permits correlation in examining situations in which specific proteins are identifiable and interrelationships among traditionally separate disciplines can be emphasized. Opportunities permitting such reinforcement in our program are obtained in considerations of collagen, certain active amines of connective tissue cells and neural elements, cell surfaces and their relationship to intercellular fluid, muscle protein and the structure of membranes.

During the first eight weeks, the gross anatomy of the extremities is studied with emphasis on the macroscopic aspects of the basic tissues. The approach is designed to consider the functionally important relationships and actions of specific areas, rather than intimate detail. Instruction in morphology during this period is aimed at relating the gross, microscopic and submicroscopic relationships of the basic tissues in a functionally oriented presentation.

Following the initial eight weeks, the student is introduced to an *integrated living system*—the cell—which constitutes the microcosm for his further studies. The red blood cell is selected as the paradigm because, despite its complexities, it is simple compared with other cells, it illustrates phenomena common to many cells but relatively easily depicted in this tissue, and it is readily accessible for study. The Red Cell Unit, as this two-week period is designated, considers the mature cell, its genesis, and its hemoglobin, as an integrated functional unit: the mature cell and its precursors providing packets for the synthesis, transport, and protection of hemoglobin, and hemoglobin itself as a specialized protein which can accept, transport and deliver oxygen to tissues and carbon dioxide to the lungs. This approach necessitates consideration of the plasma membrane, intermediary metabolism, cell development, protein synthesis, cell and protein functions, genetics, and, finally, the consequences to

the cell and to the organism when these processes go awry. During this period there is an apparently successful attempt to integrate appropriate material concerning biologic structure, biochemistry, physiology, genetics, pharmacology, pathology, and clinical medicine in a comprehensive package.

As would be expected, participation by members from up to six departments is necessary in the block and usually individuals from two or more departments participate in all discussions and laboratories.

The sequence of instruction is approximately as follows: during the first week the interdependence of membrane, metabolism, and specialized function of the mature cell is studied. First, membrane composition and ultrastructure are reviewed. The gates which control materials entering and leaving the cell are considered functionally. In this way the membrane as a regulator of cell metabolism, shape, volume and flexibility is presented; emphasis is on the dependence of the cell's survival on its physical, chemical and metabolic integrity as it is buffeted in the circulation.

Biochemical principles are presented within the framework of an examination of the cellular metabolic machinery, both from the point of view of individual enzymatic reactions and from the fashion in which reaction sequences may be linked into metabolic pathways for specific functions, e.g., maintenance of membrane integrity.

Aspects of hemoglobin—its structure, chemistry and function—are studied to show the dependence of its function on the intracellular metabolic machinery.

Following discussion of the mature red cell during the first week, the second week begins with its genesis, examining the morphologic expression of cell differentiation and maturation in molecular terms. The developing red cell is a protein factory synthesizing hemoglobin, and as such, serves admirably for studying protein synthesis. Moreover, the phenomenon that the hemoglobins produced by different individuals are not all alike and that the differences relate to genetically determined amino acids substitutions, permits use of the red cell to introduce molecular genetics.

The study unit closes with a recapitulation illustrating the interdependence of cell development, membrane, metabolism, and hemoglobin with disorders affecting these "compartments," showing how primary disturbances of membrane and metabolism affect the transport and protection of hemoglobin, and how disorders affecting hemoglobin damage the vehicle which carries it.

Following the study unit on the red blood cell, a two and one-half week period is dedicated to the principles of microbiology with particular reference to nucleic acid metabolism. The anatomy of the nucleus and cytoplasm of mammalian cells is contrasted with the analogous material of microbial life.

During the next week there is interdisciplinary consideration of membrane phenomena utilizing muscle and nerve as the functional biological study units. Conduction, excitation, contraction, relaxation and polarization phenomena are surveyed in preparation for intensive study of the biology of the organ systems.

For the remainder of the first year, organ system biology is studied in block units of time. In each of these, the gross anatomy of the system is usually

studied prior to an interdisciplinary examination involving microscopic anatomy, physiology, biochemistry and introductory clinical physiology. The organ system approach commences with cardiovascular-pulmonary biology; the next system study being the urinary tract, and general problems of acid base balance are conveniently considered by the juxtaposition of pulmonary and renal biology; other system blocks follow.

The last system considered during the first year is a general neurobiology block. This is initiated with study of the gross anatomy of the areas involved and with utilization of a programmed text in neuroanatomy. The neurobiology block occupies approximately seven weeks and includes appropriate material in the areas of neurophysiology, neurochemistry, neuropharmacology and clinical neurology. Each week specific patients are presented to illustrate pertinent aspects of structure and function in the nervous system.

Medical Biology II occupies the major portion of the student's time during the second year. During the first ten weeks there is a closely integrated presentation of principles of general pathology, immunology, virology, parasitology, bacteriology and portions of pharmacology, particularly appropriate to presentation at this time. Both classroom and laboratory periods are commonly attended by members of two, three or four departments and teaching responsibilities are such that traditional departmental assignments are virtually erased by the crisscrossing and intersecting interest of the instructors. Members of the departments of Medicine and Pediatrics, with particular interest in infectious diseases, their epidemiology and treatment participate actively during this time. A short block of time, specifically devoted to Public Health, environmental aspects of disease and Epidemiology, is interposed immediately preceding organ system blocks analogous to those utilized in Medical Biology I.

The organ system blocks vary from two to three weeks in length. This portion of the year begins with a consideration of diseases of the cardiovascular system, followed by diseases of the renal system, respiratory, gastrointestinal, metabolic-endocrine, nervous system, pregnancy and female reproduction, musculoskeletal system and closes with a one month period of Psychobiology. The individual system blocks are organized by members of clinical departments utilizing collaboration principally by members of the departments of Microbiology, Pathology and Pharmacology. An unusual feature of the block on diseases of the renal system is the utilization of the "Bricker dog" as a model system for reviewing renal physiology and studying disordered renal function (1).

The organization of the material replaces the commonly used didactic presentation of Introduction to Medicine, Surgery, Pediatrics, etc., Special Pathology and Pharmacology. A curriculum review group is responsible for monitoring content in individual blocks in order that inadvertent omissions and repetition be kept to a minimum. Although patients are commonly shown at intervals during the several organ system blocks, the orientation is not primarily "clinical" but is indeed "basic science." A few short blocks concerned with subject matter most usefully discussed outside of the organ system

approach such as neonatal physiology, teratology and cytogenetics, toxicology, and aging are also included.

Medical Biology III occupies a relatively smaller part of the student's time during the third year. It consists primarily of daily multidepartmental conferences utilizing major established areas of medical sub-specialization of common interest to the several chief clinical service divisions. Examples are: cardiovascular disease; neurology-neurosurgery; gastrointestinal system; infectious disease; hematology; metabolic-renal disease. One period a week is devoted to post-mortem comprehensive review of one or two patients from any of the several clinical services. A weekly Saturday morning conference takes a somewhat broader based view including behavioral science and sociological aspects of illness, problems of community health, a few didactic sessions on therapeutics and a monthly clinical pathological conference.

Clinical Science I, II and III complement Medical Biology during the first three years. During the first year, Clinical Science I occupies one-half day per week and is supplemented by two to three hours per week of behavioral science. The students begin to interview patients individually during their first week in school and continue to practice and develop this skill throughout the remainder of the year, gradually acquiring a knowledge of systematic history-taking and personal evaluation. During the later part of the year physical diagnostic skills are taught and the timing for this approximates the sequence of block system instruction in Medical Biology.

Clinical Science II extends for one-half day per week throughout the second year. Systematic consideration of physical diagnosis is concluded by the time the organ system block presentation for Medical Biology II begins. From this time on there is close correspondence between the two portions of the curriculum but students by now are fairly proficient in history-taking and physical diagnosis system review. A deliberate attempt is made not to limit discussion to the single system under closest examination in Medical Biology but rather consciously to consider the entire patient.

Clinical Science III occupies the principal portion of the student's time during the third year. Students are assigned for block periods of time to individual clinical services and depending upon individual circumstances are given primary responsibility for a very limited number of patients. A deliberate attempt is made to engender a holistic medical approach toward the problems of each patient irrespective of the specific hospital service. The service assignments are: Medicine-3 months; Surgery-2 months; Pediatrics-2 months; Obstetrics-Gynecology-2 months; Psychiatry-1 month.

During the fourth year it is planned that there will be a one month assignment for each student to Surgery and a one month assignment to Neurobiology. The remainder of the time will be distributed among several sets of electives. Selection of electives by students may be accomplished by individual discussion and guidance from the faculty.

Although objective evidence to substantiate subjective impression is not available, several seemingly desirable effects have been observed and associated

with this curriculum plan. Among these have been a very close knitting together of the faculty, not only in a purely instructional setting but also in research relationships. The closer working relationship established among faculty members has in turn engendered a remarkable flexibility and adaptability in the program so that variations and shifting of material from one period to another is easily accomplished. The necessity for working together with individuals from other disciplines has also probably broadened the knowledge of individual faculty members and assisted them in reviewing neglected areas or updating others. Benefits to the students may be more difficult to assess. There is a temptation to believe that the integrated approach makes each of the separate parts more easily understood. Obviously it will be many years before the true effectiveness of the program can be evaluated.

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RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D.

CASE NO. 280

A 66 year old white man was admitted to the hospital with a diagnosis of fever of unknown origin. Two weeks prior to admission he experienced sudden onset of chills and fever to 105°. There were no objective physical findings. The patient refused hospitalization and a course of antibiotic therapy was given at home. There was no relief of symptoms and the patient finally consented to admission.

Physical examination revealed a fist-sized mass in the lower abdomen just left of the midline. The patient continued febrile. Routine blood count, urinalysis, serum electrolytes, fasting blood sugar, blood urea nitrogen, and many blood cultures were all within normal limits.

A barium enema was performed and showed no intrinsic colonic abnormality. Reflux into terminal ileal loops occurred. There was superior displacement of one of the terminal ileal loops by a mass located in the lower mid-abdomen just above the sigmoid colon (Fig 1). A small bowel series confirmed the presence of a mass (Fig 2). Ileal loops were separated and there was evidence of extrinsic pressure with stretching of the mucosal folds. One loop appeared to be intimately related to the mass; a 2 cm lucent defect with smooth margins was consistently visualized in this loop and interpreted as a submucosal nodule, part of a larger mass in the mesentery.

The patient was explored and a mass was found in the mesentery of the distal ileum measuring 10 cm in greatest diameter. The bulk of the central portion of the mass was hemorrhagic and necrotic. A nodular extension of this mass reached a submucosal position in a loop of ileum. The mucosa was elevated but there was no ulceration. The mass was completely resected along with a segment of ileum and an end-to-end anastomosis was performed. The postoperative course was uneventful.

The pathologist made numerous sections through the tumor mass and reported a typical leiomyoma. Nowhere were mitotic figures seen to suggest sarcomatous transformation.

DISCUSSION

The association of a mesenteric mass with submucosal component suggests a number of diagnostic possibilities including lymphoma, metastatic carcinoma, and carcinoid, as well as leiomyoma or leiomyosarcoma. Metastatic carcinoma is often associated with obstruction, functional changes in the loops, and

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multiple areas of involvement, and of course knowledge of a primary site is helpful. Lymphoma more often shows multiple areas of involvement rather than a single focus, but localized areas of involvement certainly occur. Carcinoid



Case 280, Fig. 1. Posteroanterior view of abdomen during barium enema study shows colon filled and some reflux into terminal ileal loops. A mass is seen in lower mid-abdomen which displaces bowel loops around its upper margin (arrow). There is also extrinsic pressure on the superior margin of the sigmoid. Terminal ileal loops appear intrinsically normal, as does colon.

tumor often shows marked fixation and angulation of the bowel due to an associated scirrhous reaction.

Leiomyoma or leiomyosarcoma can be confined to the bowel in a submucosal location, grow partially into and partially out of the bowel in its endo-exoenteric form, as in this case, or be completely outside the bowel. Ulceration with hemorrhage is a very common presenting complaint in lesions high in the gastrointestinal tract. Angulation of a small bowel loop can occur with exoenteric tumors as they exert traction on the bowel. Cavitation occurs in the



Case 280, Fig. 2. Posteroanterior view of abdomen during small bowel series shows separation of two ileal loops in the lower mid-abdomen corresponding to the mass delineated on the barium enema study. There is extrinsic pressure on lower ileal loop with stretching and fixation of the mucosa along the margin (*lower arrow*). Upper loop appears to be intimately related to the mass and a 2 cm lucent defect is visualized (*upper arrow*). This defect has sharp smooth margins and is identified as a submucosal nodule, part of a larger mesenteric mass.

larger tumors and most likely would have occurred in this case had sufficient time elapsed for the necrotic mass to discharge its contents into the lumen of the bowel. For such a lesion to present solely with chills and fever and no abdominal complaint is distinctly unusual and lymphoma would certainly be more likely to produce this clinical picture.

As regards histology it is well known that the pathologist has great difficulty in establishing the benign or malignant nature of the lesion. Even though the bulk of the tumor may show no malignant alteration, a very small focus is often sarcomatous. Nevertheless, numerous histological sections were examined in this case and no sarcomatous change was evident.

Case Report: LEIOMYOMA OF ILEUM PRESENTING AS FEVER OF UNKNOWN ORIGIN.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Thomas Cassara and Dr. Sheldon B. Adler, Good Samaritan Hospital, Suffern, New York

CASE NO. 281

A six year old male child was referred for urologic evaluation following a series of febrile illnesses over a period of several months. Numerous urinalyses were normal. Prompt response to antibiotic therapy occurred with each episode of fever. During the last illness, one of several urinalyses revealed pyuria.

Intravenous pyelogram was performed (Fig 1). The left kidney was ectopic, located at the L₄-S₁ level in a paraspinous position. A 1.5 cm ovoid collection of opaque material was identified on the medial aspect of the lower left ureter at the ureterovesical junction. This was seen best on the early films and was obscured as the bladder became fully opacified. The right kidney and ureter were normal.

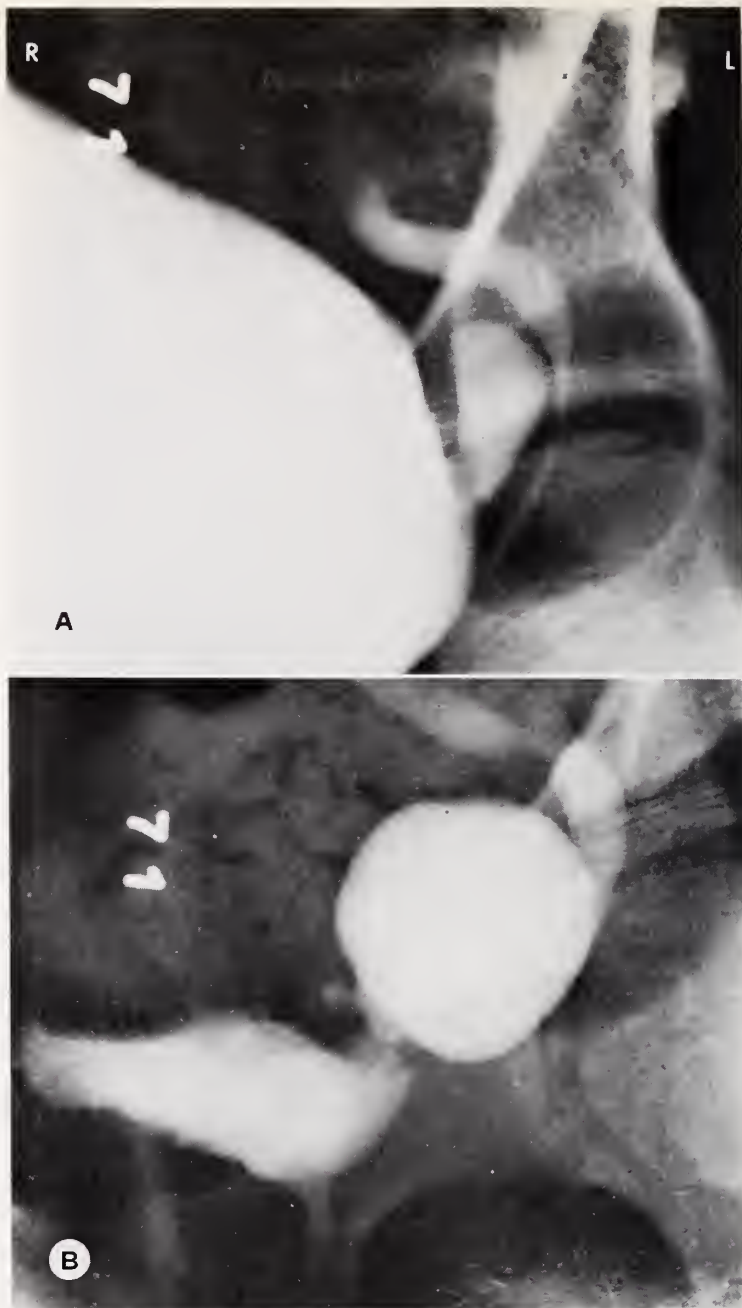
A voiding cystourethrogram was performed the following day. The patient was catheterized and opaque material instilled into the bladder. A diverticulum filled from the bladder floor projecting to the left in relation to the ureterovesical junction, and a small amount of reflux into the left ureter was observed (Fig 2a). During micturition there was prompt passage of opaque material through the urethra which appeared normal in every respect. The diverticulum became distended and a considerable amount of reflux was now observed. Following completion of micturition, the diverticulum and the ureter now emptied and partially refilled the bladder (Fig 2b).

DISCUSSION

Congenital diverticulum of the bladder is a relatively rare mechanical problem in pediatric urology. We have recently reported the radiographic features of two examples of this condition (1). Case No. 281 is worthy of note as well because of its striking similarity to the previous cases; the location and configuration of the diverticulum in each case is virtually indistinguishable from the other two.



Case 281, Fig. 1. Three-minute film from intravenous pyelogram shows left kidney to be ectopic, located at the L₄-S₁ level in a paraspinal position. Kidney margin is outlined by upper arrows. The collecting system is oriented in a gracile, "open flower" type of configuration. Lower left ureter is opacified, and a 1.5 cm ovoid collection of opaque material lies just to its medial aspect at ureterovesical junction (*lower arrow*). Right upper tract and segments of right ureter are normal. Bladder is not yet opacified.



Case 281, Fig. 2A. This spot film is made in a marked right posterior oblique projection following the instillation of opaque material into bladder and prior to the initiation of micturition. The diverticulum is opacified and now measures 2.5 cm with a relatively narrow neck. It projects to the left adjacent to lower ureter. Bladder is distended and well opacified and is partially visualized anteriorly.

Case 281, Fig. 2B. This spot film is made at the completion of micturition in a right posterior oblique projection. Bladder is nearly empty and shows normal mucosal contours; it also contains a small amount of air introduced during the catheterization. The opacified diverticulum now measures 4 cm and ureteral reflux is again observed. Opaque material from the diverticulum and ureter subsequently drained into and partially refilled bladder. Urethra was normal (not shown).

The diverticulum apparently impairs the normal valve mechanism at the ureterovesical junction and leads to reflux. Residual urine, the substrate of infection, is produced when the ureter and diverticulum empty into the bladder following completion of micturition. There is no evidence of bladder outlet obstruction in these cases and the urethra is likewise normal.

The association of congenital diverticulum of the bladder with other urinary tract anomalies is also noted. In Case No. 281 the left kidney is ectopic in its location; in Case No. 269 (1) both collecting systems were duplicated.

Case Report: CONGENITAL DIVERTICULUM OF BLADDER FLOOR.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Sidney W. Berezin, Good Samaritan Hospital, Suffern, N.Y.

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CASE NO. 282

A 35 year old man was admitted to the hospital with signs and symptoms of acute pulmonary infection. Chest X-ray revealed infiltrations in the left upper lobe and established the diagnosis of pneumonia. There was prompt clinical and radiographic response to antibiotic therapy.

An additional finding on the chest X-ray was a rounded mass in the left lower lobe which measured 40 mm in diameter. Past history revealed that this mass had been discovered seven years prior to admission on a routine chest X-ray at which time it measured 30 mm. It had been followed on repeated chest X-rays in the interim and was noted to be increasing in size slowly. A chest X-ray 19 years prior to admission had been obtained and revealed the presence of a small nodular shadow partially obscured by an overlying rib and seen only in retrospect; it measured 9 mm at that time. On all films, the mass was sharply outlined and slightly lobulated. Figures one through four illustrate the sequential appearance of the mass over the 19 year interval.

While in the hospital, laminagraphic study of the mass was performed (Fig 5). The sharp margination and slight lobulation of the mass were confirmed. There was no surrounding infiltration or satellite nodule. The adjacent blood vessels and bronchi appeared undisturbed. A number of focal, irregular, "popcorn" type calcifications were seen within the mass, all eccentrically placed. The radiographic features were felt to be characteristic of hamartoma.

The patient has always been asymptomatic as regards the mass. He had refused surgical intervention in the past, but he has consented to be followed by periodic routine chest X-ray in the future.

DISCUSSION

Hamartoma is a common pulmonary lesion. Case 282 is noteworthy, despite the fact that the diagnosis is histologically unproven, because of the

unusually long period of roentgen observation. The lesion has increased in diameter from 9 mm to 40 mm over 19 years. This fact serves to emphasize that a benign hamartoma can and does grow, albeit in a slow and regular fashion, and one must avoid diagnosing malignancy simply because of an increase in size.

The sharp margins and lack of surrounding infiltration are evidence for a benign lesion, as is the long period of observation. The "popcorn" type calcifications are typical of hamartoma and are not reminiscent of the central, laminated or peripheral calcifications associated with granuloma.

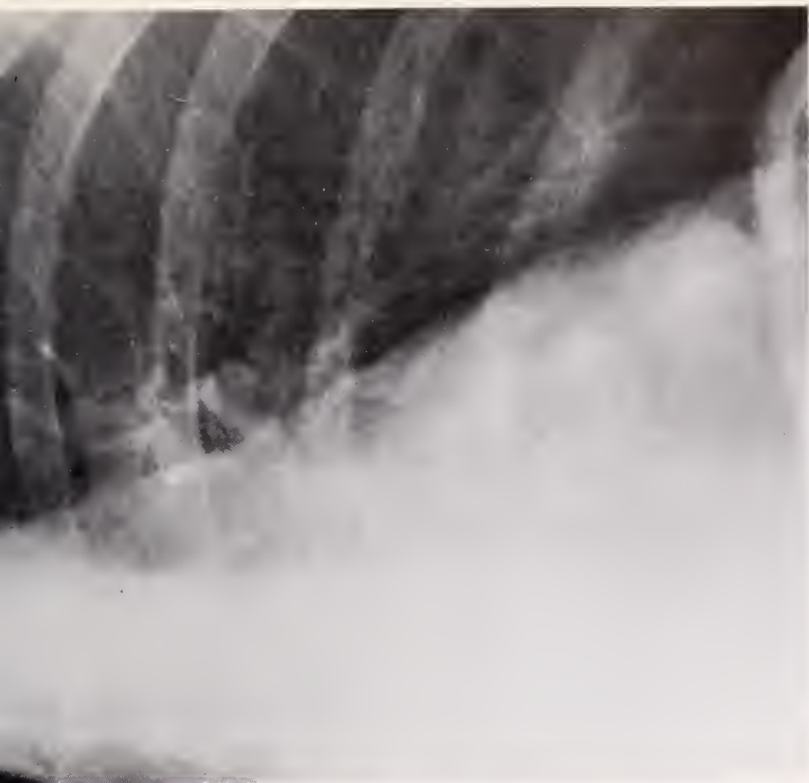
Case Report: HAMARTOMA OF LUNG OBSERVED OVER A NINETEEN YEAR PERIOD.



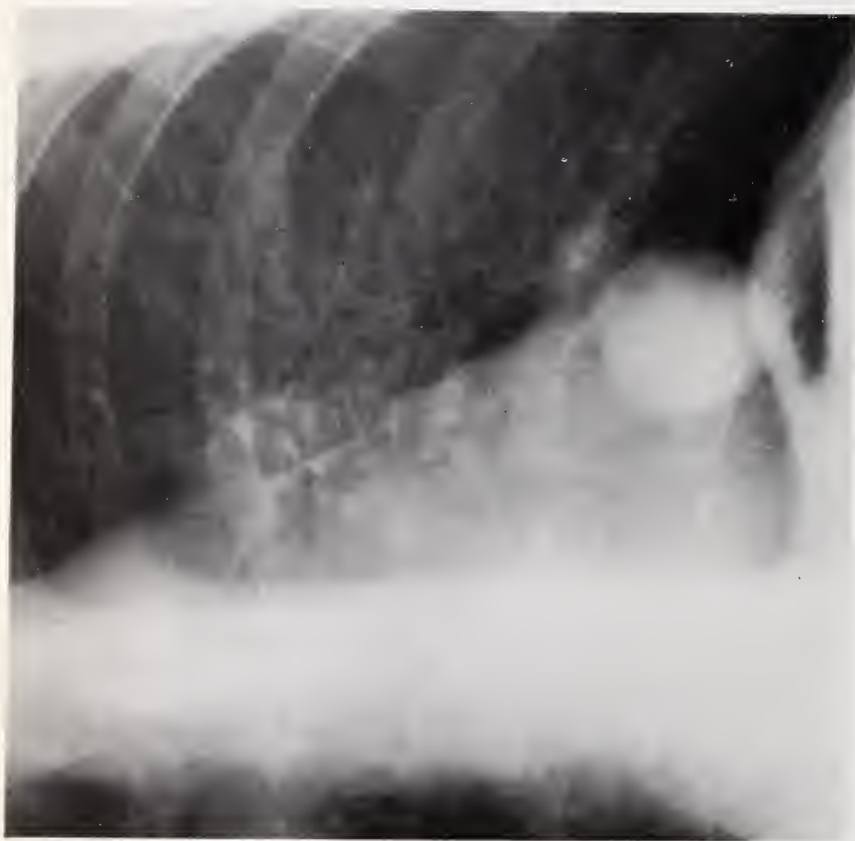
Case 282, Fig. 1. Chest radiograph, posteroanterior view, taken 19 years and 1 month prior to admission shows small ovoid nodular density at the left base which is partially obscured by tenth posterior rib (arrows). It was observed only in retrospect. It measures approximately 9 mm in greatest diameter.



Case 282, Fig. 2. Chest radiograph, posteroanterior view, taken 6 years and 6 months prior to admission shows large smoothly outlined slightly lobulated mass at the left base behind the heart. Mass measures 32 mm in greatest diameter.



Case 282, Fig. 3. Chest radiograph, posteroanterior view, taken 3 years and 10 months prior to admission shows the mass which now measures 36 mm in greatest diameter.



Case 282, Fig. 4. Chest radiograph, posteroanterior view, taken on admission shows the mass which now measures 40 mm in greatest diameter. There are infiltrations in the anterior division of left upper lobe.



Case 282, Fig. 5. Anteroposterior laminographic section through center of the mass shows lesion to be sharply marginated and slightly lobulated with no surrounding infiltration or satellite nodule. Adjacent blood vessels and bronchi appear undisturbed. Two focal, irregular, "popcorn" type calcifications are seen in the mass (arrows); others were identified in different laminographic sections. The calcifications and other roentgen features are characteristic of

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Julius Pomerantz, Good Samaritan Hospital, Suffern, New York.

CASE NO. 283

A one year old female infant was admitted to the hospital because of vomiting. In the six weeks prior to admission the mother reported intermittent vomiting of solid foods. Although at first there was some improvement with symptomatic medication, symptoms recurred and increased in severity. There were no positive physical findings on admission. Body weight had continued to increase in normal fashion and the baby was not dehydrated.

Barium swallow was performed under fluoroscopic control. Spot films were obtained followed by conventional radiographs (Figs 1, 2). A 2 cm zone of limited distensibility was present at the junction of the middle and distal third of the esophagus. A number of ingested foreign bodies were observed; the largest of these measured 2 cm in diameter and was very sharply outlined. It appeared discoid in nature as judged from films made in multiple projections. When the esophagus was distended, a thin horizontal lucent line was noted just below the zone of limited distensibility, and the large foreign body obturated the esophagus at this point. The horizontal lucent line was interpreted as a web and the zone of limited distensibility above as evidence of inflammation. The diameter of the lumen measured 8 mm between the free margins of the web on a spot film showing maximal distension. An ulceration was not identified. The configuration of the lower esophagus below the web did not suggest gastric lined esophagus or hiatus hernia. Pinchcock action at the diaphragm was excellent. When the stomach was distended with barium and filled to the cardia, the patient was placed in prone, supine and oblique positions, including Trendelenburg; manual pressure on the abdomen was included. No reflux was observed.

The patient was transferred to another institution. Conventional barium swallow was repeated (Fig 3) and cineradiographic studies were also performed. The original findings were confirmed.

Endoscopy was performed on the esophagus. A plastic wheel was wedged tightly in the lower esophagus and was successfully extracted. The diameter of the wheel measured 1.2 cm and it was 0.3 cm thick. The posterior esophageal wall was ulcerated and inflamed. A web was not identified by the esophagoscopist. A few days later a series of mercury weighted bougies up to No. 26 French size were swallowed readily and traversed the esophagus without difficulty. Following the bougienage, a regular diet was started and tolerated uneventfully. Further follow-up information is as yet unavailable.

Repeat barium swallow after esophagoscopy again demonstrated slight narrowing of a segment of esophagus at the junction of middle and distal

thirds, but this had improved and was less marked than on previous studies. No foreign body was present. One of the films demonstrated an obliquely oriented linear lucency at the expected level of the web (Fig 4). This was presumed to represent a fractured web only partially attached and floating in the liquid stream.

Case 283, Fig. 1. Right anterior oblique view of esophagus filled with barium shows a 2 cm zone of limited distensibility at junction of middle and distal thirds. The margins are smooth and an ulceration is not seen. At lower end of this zone there is a thin horizontal lucent line (between arrows). Above the horizontal line there are a number of lucent shadows which represent ingested material. The configuration of the lower end of the esophagus does not suggest a hiatus hernia or gastric lined esophagus.



DISCUSSION

It is disconcerting to entertain the diagnosis of a web when the endoscopist fails to confirm the findings. Nevertheless, it must be understood that a web can be extremely difficult to identify unless the esophagus is well distended; further, it can be easily fractured, unbeknown to the endoscopist, as the esoph-



Case 283, Fig. 2. Spot radiograph demonstrates the largest and lowermost foreign body which is very sharply outlined and measures 2 cm in diameter (*upper arrows*). This foreign body is obturating the esophagus at a narrowed zone at junction of the middle and distal thirds which represents the web. Additional lucent shadows above represent a combination of ingested material and air bubbles. A large air bubble is seen in the esophagus below the point of narrowing. Esophagus is distended maximally by the large foreign body and lower margin of the web can be seen on either side (*lower arrows*). Diameter of the lumen measures 8 mm between the free margins on this magnified spot film. Again, no ulcer is identified.

With stomach distended with barium and filled to the cardia, the patient was placed in all positions including Trendelenburg; manual pressure on abdomen was included. No reflux was observed.



Case 283, Fig. 3. Right anterior oblique view of esophagus with ingested barium showing the narrowed segment and the margins of the web (between lower arrows), similar to Fig. 1 and 2 made several days previously. The obturating foreign body has now moved upwards in relation to the web (along upper arrows). The lower margins of the foreign body create the illusion of another web.

Case 283, Fig. 4. Right anterior oblique view of esophagus with ingested barium after esophagoscopy shows slight narrowing of esophagus at junction of middle and distal thirds indicating persistent inflammation, but this is improved in comparison with previous studies. No foreign body is present but air bubbles are seen in esophagus. An arrow points to an obliquely oriented linear lucency which is presumed to represent a fractured web only partially attached and floating in the liquid stream.

agoscope is introduced. Therefore, the radiologist is often in the best position to make the diagnosis.

We believe the case presented here is one of congenital lower esophageal web in which symptoms developed as solid foods were added to the diet. Finally, with the ingestion of the large plastic wheel, symptoms became acute. The obturating foreign body caused a localized esophagitis above the web which further complicated the problem. The endoscopist successfully corrected the mechanical problem. Follow-up and repeat studies are necessary before the interpretation of fractured web given in Figure four can be relied upon with certainty.

Case Report: CONGENITAL WEB IN LOWER ESOPHAGUS.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Arnold Kramer, Good Samaritan Hospital, Suffern, New York.

Figures 3 and 4 are presented through the courtesy of Dr. Walter E. Berdon, Babies Hospital, New York City, New York.

CASE NO. 284

A five day old neonate, identical twin brother of Case 285, was well until eight hours prior to admission. Prenatal and perinatal history were unremarkable. At that time, a practical nurse caring for the baby at home reported a normal feeding and bowel movement, but following this the infant became lethargic, the cry became weak, the subsequent feeding was refused, and a question of abdominal pain was raised. There was no vomiting or diarrhea. The pediatrician was called to observe the baby and confirmed the findings. Temperature per rectum was 95°. Bowel sounds were absent. The abdomen was soft, but a question of lower abdominal tenderness to palpation was raised. The general impression was that of shock-like state of undetermined cause. Spinal tap was normal. Serum electrolytes and hematocrit were normal (reported subsequently); white blood count was 2500 and hemoglobin normal.

Plain film study of the abdomen was performed in multiple projections. There was a diminution of gas through the gastrointestinal tract. The loops were not outlined with gas in continuity as is usually seen. Some question of fluid between loops was raised because of separation of collections of bowel gas (Fig 1). No evidence of free intra-abdominal air was seen. Although an intra-abdominal abnormality was suggested, a specific diagnosis could not be advanced.

A surgical consultation was obtained. Rectal examination was performed using the little finger introduced to the distal interphalangeal joint. Some resistance was encountered. A few droplets of red blood were observed on the examining finger. Proctoscopy was performed to a similar extent. The distal 2 to 3 cm of rectum was normal, but some resistance to proximal passage of the

instrument was encountered. Great care was taken to avoid trauma during the rectal examinations.

A barium enema was performed. An adult-sized rigid plastic tube was em-



Case 284, Fig. 1. Supine anteroposterior radiograph includes abdomen and chest. Marked diminution in amount of bowel gas distributed throughout abdomen. Separation of gas-containing loops raises the question of fluid between the loops.

No mass or abnormal concretion is seen. There is no free intra-abdominal air. Chest shows no abnormality.

ployed; it was introduced into the rectum by an experienced radiologist with great care and the tip placed just inside the anal sphincter. The bottom of the barium reservoir was 30 inches above the radiographic table. Barium flowed freely from the rectum to cecum without fluoroscopic evidence of intrinsic ab-



Case 284, Fig. 2. Supine anteroposterior radiograph from barium enema examination shows barium filling peritoneal cavity. In upper abdomen note barium surrounding liver and spleen. In lower abdomen note barium located below small bowel loops and sigmoid, thus delineating the most inferior extent of the peritoneal cavity and the peritoneal reflection at rectosigmoid. There is no barium extravasated into the perirectal tissues.

normality. As the cecum was being examined, the fluoroscopist observed the barium outside the bowel in the right lower quadrant. The enema was terminated. Conventional radiographs were obtained and revealed barium throughout the peritoneal cavity indicating a colonic perforation (Fig 2). The initial spot



Case 284, Fig. 3. Supine anteroposterior radiograph of abdomen prior to discharge from hospital reveals residual barium outlining all the peritoneal surface. There is no obstruction.

film of the rectosigmoid, obtained before barium filled the proximal colon, demonstrated barium on the right side of the pelvis outside of the colon, indicating that the perforation had occurred in the region of the rectosigmoid.

Laparotomy was performed. A 3 mm perforation was found in the anterior wall of the rectosigmoid just at the peritoneal reflection. With a finger in the rectum during surgery, the perforation was established to be above the level to which the examining finger, proctoscope and enema tip had been introduced. Barium, fecal material, and plastic exudate were found in the peritoneal cavity. The peritoneal cavity was carefully irrigated, the perforation oversewn, a loop transverse colostomy performed, and the abdomen closed.

Additional history was obtained which indicated that the practical nurse had introduced a rectal thermometer to aid in the passage of gas. This was believed to be the source of the traumatic perforation.

The infant did remarkably well postoperatively. Simple film of the abdomen was obtained prior to discharge 14 days later and revealed residual barium outlining all peritoneal surfaces.

DISCUSSION

See discussion following Case 285.

Case Report: TRAUMATIC PERFORATION OF RECTOSIGMOID IN NEONATE CAUSED BY A THERMOMETER.

CASE NO. 285

A six day old neonate, identical twin brother of Case 284, was well until five hours prior to admission. Prenatal and perinatal history were unremarkable. At that time, a practical nurse caring for the baby at home reported a normal feeding and bowel movement, but following this the infant became lethargic with a weak cry. The clinical picture was virtually identical to that which the twin brother presented 24 hours previously, but not as marked, and the findings were again confirmed by the pediatrician and surgeon. Rectal examination was not performed.

Plain film study of the abdomen was performed in multiple projections. There was some diminution of gas distributed throughout the gastrointestinal tract; this was much less marked than in Case 284. There was no evidence of free fluid, free air, mass or abnormal concretion (Fig 1).

A thin soft catheter was carefully introduced into the rectum. Air was instilled and the plain film study of the abdomen was repeated. The peritoneal cavity was now filled with free air (Fig 2).

Laparotomy was performed. A 1 cm linear horizontal tear was found in the anterior wall of the rectosigmoid just at the peritoneal reflection. Relatively little peritoneal reaction was noted. The perforation was oversewn and a loop transverse colostomy was performed.

Additional history was obtained which indicated that the practical nurse

had introduced her finger into the rectum to aid in the passage of gas. This was believed to be the source of the traumatic perforation.

The infant had an uneventful postoperative course and was discharged after one week.



Case 285, Fig. 1. Supine anteroposterior radiograph of abdomen reveals somewhat sparse distribution of bowel gas, but not nearly as impressive as that noted in Fig. 1, Case No 284. No mass or abnormal concretion is seen. There is no evidence of fluid or free air in peritoneal cavity.

DISCUSSION

The literature reveals that accidental perforation of the colon and rectum in newborn infants is much more common than usually realized. At this age, all types of rectal examination are hazardous (1). These include the use of rectal thermometers, examination of the anus and rectum of the neonate with a firm catheter to exclude imperforate anus or rectum, enema to relieve constipation or meconium plug syndrome, digital rectal examination or stimulation, and



Case 285, Fig. 2. Supine anteroposterior radiograph of abdomen now shows peritoneal cavity filled with free air.

barium enema examination (2). Underlying intrinsic colonic disease may predispose to perforation such as various congenital defects, megacolon necrotizing colitis (inflammatory, vascular, megacolon), and obstruction (3-5). However, a significant number of cases occur in perfectly normal infants, thus making the high morbidity and mortality of this condition all the more tragic.

It has been shown that the peritoneal reflection over the rectosigmoid is less than 3 cm from the anus in newborn infants (1). This area is a favorite site for perforation, as occurred in both Cases 284 and 285. The risk is great, therefore, when any firm object is inserted more than 2 to 3 cm inside the anus, such as a thermometer in Case 284 and a finger in Case 285.

At first glance, the coincidence of traumatic perforation of the rectosigmoid colon in healthy twin neonates seems almost beyond belief. However, examination of the facts illustrates the preventable nature of the injury.

Case Report: TRAUMATIC PERFORATION OF RECTOSIGMOID IN NEONATE CAUSED BY DIGITAL STIMULATION OF RECTUM.

ACKNOWLEDGMENT

Cases 284 and 285 are presented through the courtesy of Dr. Sam Wilmit and Dr. Sheldon B. Adler, Good Samaritan Hospital, Suffern, New York.

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The Surfaces and Planes of Three-Dimensional Computer-Drawn Vectorcardiogram

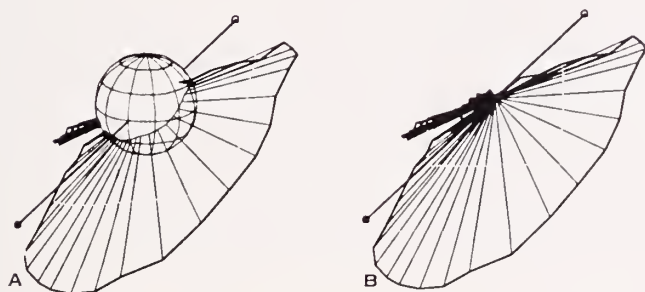
LOUIS BRINBERG, M.D.

The spatial loops of vectorcardiography are tortuous curves. They are generated by a moving vector terminus and mark the perimeter of ruled surfaces generated by the vector shaft. The surfaces approximate planes (1), which may be represented by their slopes (2, 3). These curves, surfaces, and planes are, of course, symbolic abstractions, and as they pertain to three-dimensional phenomena, their visualization demands a mental synthesis that can be difficult. They may, nevertheless, be displayed by a new technique that virtually imparts a material existence. This technique is described in detail in an article now in press (4).

The Stromberg-Carlson 4020 computer-recorder draws points and lines on the face of a specialized cathode-ray tube and does so in accordance with programmed instructions. For our purposes the instructions are as follows: given the cartesian coordinates of a vector loop, draw the loop on a spherical frame of reference of a given radius, as seen by an observer on a given axis, at a given distance, and do this in accordance with the rules of perspective.

The orthogonal components of the loop are simultaneously recorded on magnetic tape. This is passed through an analog-digital converter, a programmed IBM 7094 digital computer, and the SC 4020, which draws the pictures at electronic speeds and photographs them on paper. The entire procedure is tape-to-tape, and the same program is used for all subjects.

In figure 1a, which was drawn by the SC 4020, the sphere is graticulated at 30° intervals. The X axis is included to orient the reader. Its positive pole is marked by a solid circle, and its negative pole, by an open circle. Longitude



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is measured from the left and ranges from 0° to 180° . The anterior hemisphere is positive, and the posterior, negative. Latitude ranges from 0° to 90° . The inferior hemisphere is positive; the superior, negative. The radius is 100 units; the observer axis, -20° ; -20° (longitude; latitude); the observer distance, 3000 units. The units are those of the SC 4020. The QRS loop of a normal subject is displayed, and the T loop is seen on edge to the west.

Planes that pass through the center of a sphere intersect the surface on great circles. The points at which the instantaneous vectors emerge from the sphere are joined to form a curve, and the compliance of this curve with a great circle indicates the planarity of the ruled surface. In this case the planarity is evident, and the steepest line in the plane, which is its slope, is estimated to be at 10° ; 25° (bearing; dip). This means that the plane of predilection dips towards the 10° meridian of longitude and that it dips 25° from the plane of the equator.

The completed surface and curve are displayed in figure 1b, in which the sphere is reduced to a point.

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Erratum

Through typographical error the words "usually and on occasion" were omitted from the article entitled "Diffuse Small Intestinal Abnormality due to *Giardia Lamblia* with Roentgen and Clinical Reversibility after Therapy" which appeared in the March-April issue of this Journal on page 116. This omission erroneously changes its sense. The correct rendition should have been:

"It is known that *Giardia lamblia* infestation is usually asymptomatic in the host and produces no demonstrable change in the body of the carrier. It is also known that on occasion it produces distressing symptoms in the patient harboring it (1)".

ARCHITECTURE OF MEDICAL SCHOOLS

Physical Facilities for the Educational Program

George T. Harrell, M.D.

Education in medicine concerns the study of human biology in all of its aspects. The physical facilities should reflect the philosophy of the institution and the educational program to be developed. The facilities should provide spaces specifically designed for teaching, patient care, and research (1).

The teaching spaces should accommodate all types of students who may be taught in the physical plant both from the point of view of the scientific background and the clinical art of medicine. The college of medicine is the focal point of the medical center and its primary responsibility, as conceived by the public, is to train physicians for practice. The service rendered to the community in which the medical school is located is usually given as patient care. The type and amount of patient care should be tailored to the educational needs of the institution and not be allowed to overwhelm the training program.

Medicine requires a never ending process of self education. The emphasis should be on the subjective learning process of the individual, since he must continue to study throughout his entire professional life. Medical practice is an art which rests on a scientific base but the base is continuously changing as the result of the rapid increase in knowledge accumulating through research. Research can be considered an integral and essential part of the educational program.

Public expectations from medicine have been rising rapidly. With the control of supplies of food and water and the institution of public health measures for prevention of pollution of the environment by sewage and toxic wastes, the public tends to take for granted conditions for safeguarding health. Immunization against epidemic infectious diseases and chemotherapy for treatment of acute episodes of infections are prolonging life and changing the character of illness. The public has come to expect health as a basic human right. It is not satisfied with the cure of illness after it has occurred, but is insisting on the prevention of illness, to assure its absence, so that the individual can lead a full, effective, and satisfying life. The educational program must look toward the community for some aspects of training and this responsibility has implications for facilities.

Medicine as a University Discipline

Medicine has been considered a true university discipline since the Middle Ages. The educational program in medicine should be a continuum and ideally

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should begin with preprofessional training and extend throughout the professional years of the curriculum. Because of the length of the educational sequence and the multidisciplinary nature of the scientific base, the educational program can best be conducted on a university campus. Even though several of the new schools are not physically placed on the main campus, they are being developed as university activities. Most of the new medical schools, however, are being placed on the campus of established universities.

A few efforts are being made by new medical schools to explore the possibility of shortening the total educational sequence. Other educational experiments are exploring the value of overlapping or interdigitating courses taught by the faculty of arts and sciences with those taught by the faculty of the college of medicine. These efforts usually do not require additional facilities. Medical schools are developing graduate programs in the basic medical sciences leading to the research degree, Doctor of Philosophy. This parallel program requires different facilities in terms of laboratories and requires general university resources of a basic nature which can be furnished by departments located on other parts of the campus and need not be duplicated in the medical center.

Increasingly, postgraduate education in both basic science and clinical disciplines is being included in the educational program at the postdoctorate level. The training of interns and residents who are postgraduate students in the clinical disciplines is being recognized as a university responsibility. Facilities for this training are easily incorporated in the teaching hospital. More attention is being given to the medical school's responsibility for continuing the education of the physician after he is in practice and has completed his formal training in the university or teaching hospital. A separate facility of lecture and conference-seminar type will fill this need.

Increasingly, medical schools are assuming the responsibility for portions of the educational program in the allied health professions such as dentistry, nursing, pharmacy, the medical technologies, and social and behavioral sciences applied to medicine. Many other training programs at the subprofessional level are being developed but would not require highly specialized physical facilities for training. Much of the training is "refresher" in type and can be done by lecture and in-service work.

With this expansion of the educational concept, medical schools are becoming the focal point of medical centers, or with the change in public expectations in recent years—health centers.

Facility for the Scientific Base. The scientific base on which the practice of medicine rests is a continuum of knowledge with the administrative divisions into specific disciplines arbitrary and overlapping. The facility for this portion of the educational program is usually called a medical sciences building and it is in this unit that student teaching at the professional level begins.

The medical student should have a study area which emphasizes the individual approach to learning; study cubicles have been successfully used for this purpose (2). The professional attitude of the student is formed in these early years. The physical facilities should help the student to recognize that

the educational program is training him in the intellectual discipline of the scientific method and in helping him to apply this method to the development of problem solving techniques he can subsequently use in patient care. The faculty can support him in the learning process, teach him manual and intellectual techniques, help him develop inquiring critical attitudes and show him how to use educational and patient care resources which subsequently may be available in the community where he practices. Specific facilities should be provided for the interaction of medical students with faculty, with each other, and with other students in the medical center. Small areas decorated in an informal character scattered throughout the physical plant in relation to vertical and horizontal student movement would promote this interaction.

Medical students often work in groups of four for gross dissection of the human cadaver, animal experiments, autopsies, and other teaching activities in the preclinical years. A convenient group for discussion, seminar and demonstrations is 16. Many new schools are starting with classes initially in the range of 16 to 24 which will be gradually increased each year. Several of the new schools plan to limit the class size for a number of years to 64 entering medical students. The size of the entering class in this country in the past few years has been in the range of 96. With the pressure for the training of more physicians and the availability of construction funds, the average class size is now approaching 128.

The scientific base of medicine is continuously being strengthened through research which is conducted and supervised by the faculty. The faculty in the basic medical science departments and the full time clinical faculty members need the same type of office and research laboratory space. The faculty facilities are usually grouped for convenience into administrative units which may be departments or smaller divisions. Departmental administrative space should be conveniently located for student access. Each department or administrative unit should have facilities for seminars and conferences which can conveniently also serve as departmental libraries. Whether the research facilities are separated into a block of space for convenience or scattered to make them more readily available for students is a matter of the program of the school. Graduate students in the basic medical sciences need laboratories for the research work necessary for the thesis. The study function for graduate students can be incorporated into the research laboratory or can be provided in a centralized study area through the provision of cubicles. For the first year of the graduate program when course work is emphasized, some advantage in interaction can be obtained by placing the study function with that for medical and other students.

The basic research program of the school involves the use of test tubes, instruments, and animals to a greater extent than it does the human being. The requirements for flexible space, particularly to accommodate the mechanical requirements, are much larger than in any other type of university construction. The mechanical provisions as well as the basic architectural design should provide for continuous alteration in research laboratory space. Research equip-

ment is becoming ever larger, more complex with more exact requirements for control of temperature, humidity and ventilation. Indeed, planners would be well advised to start with the mechanical requirements which might ultimately be envisioned some years after completion of the building and to develop the design of the building around them.

Shared Facilities. Many educational facilities can be shared by all departments in the medical school. The laboratory phase of preclinical teaching currently is emphasizing a multidisciplinary approach. Multidiscipline laboratories should provide both stand-up and sit-down laboratory bench space for each student, unassigned space for special instruments and reagents, a room for large and noisy equipment which could be shared by groups of students, and a preparation area (3). Multidiscipline laboratories increasingly are being administered as a central educational facility for the entire school (4).

The library is a key central facility around which the educational program at all operational levels revolves. It should be placed for ready access by both the basic science and clinical disciplines.

Animal facilities should be centralized for ease in administration, quality control, and reduction in the expense of operation. Several schools have developed separate long-term quarantine, holding and breeding units of farm type (5).

Some new schools are planning a division of educational resources which will include audiovisual facilities both for production of teaching aids and demonstration of them to students. The traditional department of medical illustration, art or photography would be included in this division. The role of programmed instruction at the individual level through "teaching machines" or computers programmed for teaching might also be a responsibility of such a division. Whether these facilities are located in a separate part of the physical plant or are located in or adjacent to the library, will depend on the program of the school. It is technically possible to incorporate some facilities of this type into study cubicles, but whether this is wise in terms of the formation of student attitudes is questionable. The danger of developing a mechanistic rather than a warm human approach to education of the individual student must be considered.

Some teaching is still best done in large groups by lecture or demonstration techniques. Provision for both front and rear projection of lantern slides and opaque material, television by monitors or large screen rear projection, chalk boards, and space for demonstration of patients should be provided (6). Facilities of auditorium type large enough to hold several medical school classes, house officers, and other interested students or staff in the medical center should be provided close to patient care facilities. Clinical auditorium facilities should provide for presentation of patients in bed or wheelchairs as well as for audiovisual material.

Maintenance and scientific instrument shops can be most effectively organized as centralized facilities. The extent of the shops will depend upon the location of the physical plant in relation to the rest of the university and the

extent of cooperative programs such as biomedical engineering which have been developed.

Fiscal operations including purchasing, personnel, grants management, house-keeping, and operation of the physical plant should be centralized in space specifically designed for administrative purposes.

Facilities for the Art of Practice. The ultimate goal of the educational program is to train the medical student in the care of sick people. The practice of medicine is a highly confidential interpersonal relationship between two individuals—the physician and his patient. Man is an individual who is a member of a family which lives in a community. He is a social being who has his own sense of values of tangible and intangible factors which alter how he leads his life. Conflicts induced by disease or by stresses at work, at home within the family, or within the community may be reflected in symptoms of illness or functional overlay to underlying organic diseases. Behavior, therefore, should be considered a basic biologic phenomenon in which the range of variation of normal and the variation in behavior with age must be known before the effect of disease can be interpreted. Though this teaching may begin with animals in the basic science years, the ultimate application is to people so that facilities should permit demonstration of normal and sick individuals at all age levels.

Clinical facilities are necessary in which the application of the scientific method to individual patient care can be demonstrated. The physician should take a multidisciplinary approach which brings into programs of patient care physicians with different clinical interests and auxiliary workers with different types and degrees of training. Increasingly, behavioral and social scientists, engineers, basic research scientists are being incorporated into the educational program. Most clinical training in the past has revolved around an acutely ill bed patient in a teaching hospital. The hospital should have nursing units, operating rooms, delivery rooms, and other facilities for intensive care (7). Most hospitalized patients require an intermediate level of care and are confined to bed. To improve the educational program, at least one new medical school is planning nursing units composed of single rooms. Single rooms offer the greatest privacy for the patient in the taking of the history, performance of physical examination and for many necessary procedures. The size of a nursing unit in which a team of doctor, nurse, house officer, medical student and paramedical personnel can effectively work is in the range of 15 to 30 beds.

A minimal or self-care unit should be provided for those patients who do not need to be continuously in bed but do require some time there. This unit can be used for convalescent patients who have progressed so that they do not need full nursing care, and for ambulatory patients whose treatment does not require bed care. Patients who need multiple diagnostic procedures which require preparation, serial samples during performance of tests, or long-term observation can be housed in such a unit (8). This atmosphere is also good for patients undergoing extensive long-term rehabilitation after accidents, surgery, or acute illness. The facility could be decorated to resemble a home and could provide for a member of the family to stay with the patient.

Facilities for care of psychiatric patients often are best placed in an area designed for ambulant patients so that they tend to look out toward the community and not in toward the institution.

The conditions of medical practice in this country are changing. Traditionally, the physician has practiced independently and most medical care in this country is still given by physicians to ambulant patients seen in the office setting.

Facilities for ambulant out-patients for short or repetitive visits usually are designed in the medical center to function as a clinic. In some areas of the country, particularly in large cities, the out-patient department has been used by the patient as a substitute for a family physician. Increasingly, medical care is being organized through group practice clinics. The out-patient department can serve as a model for this future phase of practice.

The emergency room serves out-patients, but should be physically distinct from the clinics. It should not be designed as an off-hours out-patient department. It should be planned for the care of accidents which are an increasing cause of death in all age groups, the treatment of acute episodes such as poisonings and suicides, as well as the usual run of medical illnesses.

The character of illness is changing. In the past, the physician saw a series of acute infectious diseases about which he could do little. Now the chief causes of death and disability are chronic degenerative diseases which often have a genetic basis. A facility of limited size for the care of chronically ill patients who need to be in bed part of the time and ambulatory part of the time should be included. This facility advantageously may be built as a separate unit in the character of a nursing home. These patients require long-term if not indefinite care, many times for the rest of their lives. Long-term care of chronic illness should provide a setting in which the student can see good medical care rendered without all of the facilities of the teaching hospital immediately at hand.

More facilities for small group discussion and conference are needed in the clinical areas than in the basic science units. Facilities for presentation of patients and for group study should be provided on each nursing unit, the ambulant facility, and in the out-patient clinics.

With the change in the character of illness, more use is being made of laboratory procedures. The technical procedures performed as part of patient care are increasing in complexity and are involving more mechanical devices of increasing sophistication. The hospital laboratories and such research laboratories as are built in the teaching hospital should incorporate flexibility in architectural and mechanical design to permit ready change in function and inexpensive installation of new equipment in the future. The facilities must provide for expansion in terms of numbers of tests and size of equipment. The approach to patient care involves a synthesis of many basic scientific disciplines, particularly chemistry, physics, and biology so that the physician must take a multidisciplinary approach. With the increasing use of laboratory tests, a program of quality control should be instituted, with the result that the

technicological aspects of medical practice become increasingly centralized in institutions of which the highest development is the teaching hospital.

This trend poses a dilemma for the physician. How does he adjust to the interjection of an institution into an interpersonal relationship? How does the patient adjust to the potential loss of confidentiality of data as increasing use is made of mechanical devices for storage and retrieval of information concerning his illness? How can the student be educated to be at the same time an objective, dispassionate scientist and a warm human being interested in the patient as an individual? Both approaches are essential in good patient care. Some schools are experimenting with a Department of Family and/or Community Medicine where the impact of disease on the family unit can be studied and where teaching can be conducted outside of the medical school in the community itself. The office base for this educational unit should be in or adjacent to the teaching hospital.

The educational program directed toward training for the practice of medicine is concerned, therefore, with the development of a pattern of thinking in the student. An approach to problem solving that employs the scientific method on a base of the medical sciences is essential. The faculty serve as role models for the student, and the various facilities for the art of practice serve as prototypes of the facilities he ultimately will use in his own practice in the local community. The integration of knowledge still must be accomplished by the individual student, hence, facilities for individual study must be provided in the clinical facility. The study cubicle utilized for medical students during the basic science years can also be used in the facilities designed for the practice of the art. Since house officers are post-graduate students, they need a unit for individual study. House officers serve as teachers and junior faculty in the instruction of medical students and thus have educational responsibility as a part of the learning experience. The study cubicle designed for medical students has been found extremely valuable in filling the need for a base of operation for house officers, and should be placed in the facility between the clinical department space and the nursing units.

The research approach to clinical patient care should be fostered. The hospital laboratories can be looked upon as a multidisciplinary facility for the education of medical students in the clinical years, house officers, and paramedical personnel. If all laboratories used for the study of patients are grouped together, several advantages will accrue. To be maximally effective, the equipment in a given hospital laboratory should be used by all clinical services requiring such facilities. This arrangement would tend to focus the attention of the student on an approach to patient care in terms of the system involved in a specific disease process. A tendency might develop for him to become oriented later in the curriculum toward this specialized approach and to lose sight of the patient as a whole. Proper planning of the curriculum, the use of ambulatory facilities from a general or multidisciplinary point of view should counterbalance this tendency. The introduction of the student to patients early

in the curriculum through the Department of Family and Community Medicine or some other teaching device also should guard against this danger.

If the patient laboratories are grouped together by physiologic systems and are recognized as multidisciplinary in character, the administration of individual, clinical departments may be put at some disadvantage and might lead to less autonomy of individual clinical departments. A strong chairman and regular departmental conferences would reduce this danger. The offices and basic research laboratories for clinical faculty can be provided either in the medical sciences building or teaching hospital, and can relate to a system oriented grouping of hospital laboratories.

Some schools have designated specialized core laboratories with a limited number of associated beds as a distinct clinical research center. The same educational objectives can be achieved, however, in the arrangement described above.

All of these clinical facilities can be incorporated into a university teaching hospital, whose emphasis is on the educational program, with size limited to the number of patients needed for the teaching program. Teaching hospitals tend, therefore, to be smaller than community hospitals.

Housing. With the increasing tendency of medical students to marry early and to have children while in training, adequate housing should be provided. This housing usually takes the form of apartments with play space for the children. Ideally, student housing should be located on campus where the medical student can meet informally other graduate and professional students. Housing for students in the clinical years of the medical curriculum and for house staff should be within five minutes walk of the teaching hospital so that the use of automobiles and provision of parking spaces is reduced.

Indoor and outdoor recreational space for physical activity and mental relaxation is necessary in any educational facility. It could be appropriately related to the medical sciences building, teaching hospital, or housing depending upon site.

Particularly where the medical school is located in a small or isolated community, adequate housing for faculty may be necessary in order to recruit the caliber of faculty needed. Housing on the campus provides an opportunity for faculty to mix with students in the medical center and faculty from other disciplines informally.

Site. These requirements for educational facilities of various type and size emphasize the need for an adequate site. If the medical sciences building and teaching hospital are built as a continuous unit, the number of acres required on the site may be considerable. The advantage of having an animal farm on the same site increases the required number of acres. A large site rarely can be achieved by a program of urban renewal, hence, most new medical schools are being built on the periphery of the campus or the city. Patients readily can reach the teaching hospital by bus or car.

SUMMARY

Medical educational facilities should be designed to teach both the science and art of medicine. Specifically designed teaching spaces should be provided for individual learning and for group instruction. Clinical facilities for care of patients with various stages and types of disease processes should be provided. Research facilities for faculty and students are essential as a part of a modern medical facility.

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The Versatile Laboratory

Edra L. Spilman, Ph.D.

The original concept of the multidiscipline laboratories (M-D labs) came from Dr. Chauncey Leake in 1927. Fifteen years were to pass before the first medical M-D labs were started at Western Reserve University in 1952. These laboratories differed from the classical physical plant in two respects. First, the number of students in each M-D lab was limited to sixteen, and, second, both sit-down (low) and stand-up (high) work areas were provided (1). The latter provided suitable facilities for the spectrum of laboratory exercises involved in undergraduate medical education. In 1955 M-D labs were established in the School of Medicine at the University of Southern California. An important modification incorporated into these laboratories was the so-called interlab. Each pair of 16 man M-D lab modules was constructed to abut a long narrow room in which hoods and other larger pieces of equipment could be more or less permanently installed. Further, the low and high work areas were relocated so that an open center aisle became available for use as a conference area. Stanford University School of Medicine soon followed (1959) with M-D labs having the interlab located between pairs of 16 student modules (2). Stanford University also modified the type and location of the laboratory furniture to suit their particular teaching objectives. Since 1959 M-D labs have been established throughout the world. Many are now under construction in the United States and many medical, dental, nursing, and other schools are evaluating M-D labs in terms of their projected teaching programs.

The functional advantages of M-D labs over classical laboratories (1) were originally conceived as: 1. provision of a single work area in which all types of laboratory exercises could be performed; 2. assignment of a "home base" to the medical student; and 3. centralization and coordination of laboratory logistics and supporting personnel. Stanford University has extended the first of these functions to include the laboratory project concept wherein the students developed several laboratory projects under faculty supervision. The success of this program demonstrates that the M-D labs are adaptable to use by students for semi-independent investigation. In 1962 Northwestern incorporated the gross anatomy dissections into the M-D lab module by constructing crypts under the high bench (3). Western Reserve University had been using their M-D labs for infant cadaver dissection but had continued the gross dissection in a separate facility.

The evolution of the M-D labs into a more and more viable adjunct to the learning environment must inevitably continue. M-D labs should not be

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constructed without careful review of potential future uses. In most instances this approach has been followed in the newer facilities now under construction. However, many laboratories are being designed with only minor modifications of existing modules. Changing emphasis in educational approaches such as the laboratory project may necessitate provision of newer types of back-up facilities. Programs leading to greater involvement of the student in his education may also require specially designed facilities throughout the laboratory in order that the full potential of the program be realized. The application of technology now well developed by the television broadcast industry and subject to considerable research by certain corporations with divisions in educational applications could well revolutionize graduate educational methods in the near future. Much of this technology is in use in primary and secondary schools. Acceptance above this level is just gaining ground.

The M-D labs can provide the ideal environment for the various types of supplementary teaching and learning aids as they may now be visualized. In contrast to the lecture room the laboratories permit unrestricted movement and better opportunities for verbalization. The student can make use of different types of aids which may be either fixed or portable. The sixteen student module is small enough for noise levels to be kept minimal and yet large enough to limit capital investment. The use of modified laboratory-study carrels or cubicles can give some degree of privacy and considerable flexibility.

A case could be made for installing teaching aids in a library environment instead of in the M-D labs. The normal library environment requires minimal commotion and noise. Separate facilities might be needed to maintain this. Students tend to use supplementary teaching aids as individuals and in small groups. Carrels or cubicles in the library would have to be large enough for these variations in group size. It might not be desirable to construct one carrel per student because of space and cost limitations and because of possible low usage. Libraries should provide some extra private areas such as carrels or cubicles, yet, as the potential of these areas is increased, use may be increased and more carrels might be needed. Further, a good balance might be difficult to predict. Provision must be made to reduce noise and commotion levels arising from the increased traffic. The laboratory solves all of these problems since the student already has a home base there.

Separate banks of carrels or even larger areas not associated with the laboratories or library could also be equipped for student use. However, again the question of numbers arises. The student already has the laboratory, lecture room, and library as learning points. To these must be added desirable locations outside of the institution; i.e., the home, dormitory, etc. (6). The construction of another separate function should be well justified by experience or commitment. Proper design of laboratory facilities might well limit the need for separate carrels.

The Laboratory Project. The laboratory project concept involves the development by the student of an experimental attack on one or several well-defined and well selected problems. For instance, Stanford University School

of Medicine includes as an important part of its program such projects as the isolation and characterization of an enzyme such as hexokinase, the isolation and synthesis of deoxyribonucleic acid, and others. Western Reserve University School of Medicine uses projects involving a carbon balance study of a micro-organism metabolizing glucose, the elucidation of the gene-enzyme relationships in the biosynthesis of the aromatic amino acids in the yeast *S. cerevisiae*, a study of bacteriophage genetics, and other projects.

The approach for the student in these projects is closer to exploratory research than to pre-planned experiments. The students working on each project are carefully supervised so that guidelines of scientific methodology are observed. The project begins with consultations with the instructors and with library research. The students devise a protocol and evaluate it carefully with an instructor before initiating the laboratory work. After completion of the experimental work the students prepare a report. Selected reports may or may not be presented for whole class discussion.

The use of laboratory projects as a teaching tool in an improperly designed and equipped laboratory can create problems in logistics, inventory, and back-up facilities. Each of these will be discussed separately. Heavier demands may be made on faculty time, and the need for good training for the supporting staff in the M-D labs may soon become apparent. The latter are problems of more ready solution and will not be discussed.

Since the number of approaches to a given laboratory project can be equal to the number of student participants, a flexible logistics support is essential. A saving factor has been the desire and ability of instructors to guide the student along a few well circumscribed approaches. The M-D lab staff must be prepared to supply a wide variety of material on relatively short notice. Much of this material can be predicted, and, after a given project has been used a few times, inventory supplies tend toward routine.

Much of the equipment needed for projects may be considerably more sophisticated than that normally found in M-D labs. Programs for acquiring such equipment must be initiated and interim supplies must be reserved within the institution. Most research workers regard student use of research equipment with disfavor. Since the instructor is usually selected because of an active interest in the area of the laboratory project, he usually can aid by permitting the use of his research laboratory equipment. In any event, the equipment to be used in the M-D labs inevitably must be upgraded. Stanford University has made excellent progress along these lines.

While the students may be required to perform some experimental operations only with supervision; i.e., high speed centrifugation, scintillation counting, etc., the student should be given the opportunity to work at any time as required by the project or by his inclination. The latter periods may fall outside the working hours of the supporting personnel. Hence, contingency provisions must be made for the student to obtain or have access to equipment and material. This can be done by advance requests and sign-outs or by use of open stockrooms. The development of respect and responsibility for equip-

ment then becomes essential and this can be an important aspect of laboratory project teaching.

The success of the laboratory project is closely related to inventory control. For instance, laboratory projects involving microbial genetics can involve hundreds of petri plates of media. Some lead time is required for preparing and maintaining adequate stocks. Similarly, sterile glassware preparation, the supplying of adequate stocks of chemicals, and the processing of unexpected loads of used glassware require careful inventory management. Such control might best be handled by assigning one or more technicians as "inventory clerks." To them would be assigned the responsibility for keeping supplies moving into and out of storage and work areas through continuous inventory.

The types of back-up facilities needed for teaching pre-planned laboratory exercises have already been described (4). It is desirable that further facilities be provided if laboratory projects are planned. The laboratory itself should remain fairly clear for concurrent work on necessary basic laboratory exercises. Many types of equipment and accessories can be accommodated in an interlab but would necessitate reduction in counter areas and provision of open wall areas and a carefully balanced relationship between the two. These open areas could be used for larger pieces of equipment which might be rolled in for temporary use; i.e., fraction collector, respirometer, polygraph, oscilloscope, centrifuge, etc.

The desirability of having equipment rooms other than the interlab should be considered. These could be satellite rooms near the M-D labs in which equipment designated more or less specifically for laboratory projects could be permanently located. Thus, the equipment could be safely stored during off periods. Such facilities are common in research departments.

The cold room areas might well be separated into storage cold rooms and working cold rooms. Sizes will be governed by anticipated use. A sub-zero cold room might still double as a storage-work room.

The inclusion of several undesignated rooms would take care of such difficult-to-predict operations as chromatography (explosion-proof, corrosion-proof), dark room activities (plating microbes, photography), U-V exposure, etc. The M-D lab module and the interlabs may not be desirable locations for such activities.

Television, Rear Screen Projectors, Continuous Film Projectors, Student Response Monitoring, Computer Storage and Retrieval. The scope of self-study aids seems to be limited only by the imagination. Contrary to the opinions of many teachers, self-study aids are not necessarily intended to be replacements for direct contact with the students. Direct teaching will long remain the method of choice at all levels of education. The use of various electronic media is intended to supplement and reinforce the efforts of the teacher. Programmed texts and carefully planned audiovisual-television material can be used for the presentation from a most basic idea through to exercises involving the application and use of information. The M-D lab can provide the environment needed for the use of these instruments. Here the student can

participate in his own learning experience to the extent that he wishes and at his own pace.

A television monitor has many applications, particularly in the demonstration of techniques. There is wide experience in the dental teaching applications—the camera can place every student equally close to the patient. Demonstrations can be given for the various types of tooth repair, for making impressions, and for examinations of pathologic findings. Similarly, anatomic and neuro-anatomic dissections can be performed step-by-step by an experienced instructor with subsequent dissection by the student at his work table. Experience has shown that these demonstrations should be short, approximately five minutes, with the student period being fifteen to twenty minutes (5). Student interview techniques can be recorded on videotape for subsequent playback and evaluation (5). Instructions in the use of relatively complex equipment can be given by closed circuit television to provide a flexible method in contrast to filmed instructions which are fixed and which cannot be readily changed or corrected as the need arises. The applications of television in surgery are well known. Further, routine lectures and special lectures can be stored in a computer together with illustrative material for retrieval by the student at a later date. The option could be given for retrieving all or only a part of a given lecture. Programmed material can also be stored for retrieval as desired.

Portable rear screen projectors and continuous film projectors could provide a wealth of supplementary material for lecture reinforcement. They work well in lighted areas and can handle 8 mm sound or silent films, and, in some instances, can be used with slide carriers having accompanying sound tapes. Much of the material to be used in these projectors might have to be developed in the particular institution specially for the teaching program. However, some commercial material is available. All cartridges and slide carriers could be issued just as books from the medical library.

The equipment required at the student area in the M-D lab for these aids would include the television monitor, the telephone linkage to the computer for stored material, and shelf space for the projectors. An audio system for communication to the central television pick up area and a signal system would complete a versatile package.

Programmed computer instruction with variable student response may not lie too far in the future. The hardware is available and the limited supply of software may be overcome by a concerted effort on the part of the institution involved to develop programs according to the emphasis and requirements of their curricula. With supplementary teaching aids of this type, cost factors begin to play a more important role. Installations could be made at some one point in each M-D lab module, in one or more of the back-up rooms, or in the library.

Conduits to the M-D lab student units should be large to accommodate the electronic aids of the future; however, it must be appreciated that the turnover rate of physical facilities used in medical teaching may well increase. Obsolescence will be the rule rather than the exception.

A small library consisting of general and specific reference books and texts as well as mathematical tables, chemical tables, etc., can be of great value in the versatile M-D lab module. Students may keep their personal texts and reference books in other locations as well as at their M-D lab desk. Having ready access to material pertinent to the areas of study could be most helpful to a student who has found that a desired reference book was left at home. Even though the main library may be close by, the time needed for the trip would be saved.

Some general operating regulations would be needed to prevent the loss of books, continuous film cartridges, tapes, and other materials supplied in the M-D lab. No supplementary teaching material should be permitted to leave the module. All material should be returned to the central storage area immediately after use and there should be no storage in the student's desk. Damage should be reported immediately so that corrective action can be taken. The student would recognize that regulations of this type are for his benefit and would respond accordingly.

As the search continues for more effective methods for teaching and for learning the need for more active participation by the student becomes increasingly desirable. The long era of lectures and pre-planned laboratory exercises followed by independent study may well be supplemented by methods which permit a greater choice for the student to actively participate in learning and in problem solving. As in any transition the initial demands on time and imagination will be great. Once the procedures are established, the programs devised, and administrative problems solved, the task becomes easier. Then, continual updating will be necessary and improved technology must be followed until the next great upheaval occurs. The extensive attention now directed towards educational methodology may well cause a change in the turnover time for facilities, instruments, and approaches. Educators must ever be alert for these advances.

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What Kind of Architecture for Education for Health?

Joseph Blumenkranz, A.I.A.

The Encyclopedia Britannica defines modern architecture as follows:

Modern Architecture is an attempt to interpret man's purpose through his buildings in a style free in relation to change and independent of fixed symmetries. . . .

The Modern Architect must provide for the many changing needs of practical, swift-moving life, and interpret present-day living with prophetic foresight, making architecture a plastic part of living.

With rare exceptions, buildings designed for the health sciences miss this definition; instead, they reflect the prevailing faddism which produces clichés which have little to do with solving the problems posed by the strides in medicine. Moreover, in most cases, the architect is hamstrung by budgetary restrictions beyond his control. These budgets are usually arrived at by sponsors who base their estimates of cost on previously built projects which, in turn, represent seriously underfinanced capital investment. Thus, the inadequacy of capital funds is self-perpetuating.

Evaluating a structure in the health field, one misses frequently a basic logic which should have been, but failed to be, responsible for its outward form. The appearance is rarely, if ever, ascribable to the elemental internal organization. There is often a disproportionate emphasis on the visual impression of the building rather than on an esthetically pleasing appearance which also satisfies functional requirements.

Unfortunately, this "facadism" reflects the lack of sense of reality by a great segment of this country's architectural profession. In 1966 in the U.S.A. alone about two billion dollars were spent on capital construction for health facilities. Lack of realism, on such large scale, can be appalling and wasteful.

Moreover, those concerned with planning fail to emphasize the demands on architecture made by the advances in medicine. New challenges are yet to be met in the field of medical education as well as in the physical facilities for education. We are living in a period of rapid change; while change is one of the few constant factors in the life process, we have yet to become adjusted to its new pace. The problems which face architects are an outgrowth of the unprecedented rapidity of change, growth, and development. Boundaries between disciplines and departmental barriers are crumbling. Subject isolation gives way to conjoint teaching. Intercommunication is recognized as essential. Experiences are constantly exchanged.

In the past, vast medical complexes grew with the identification and evolution of new disciplines, imitating in growth the pattern set by their mother university, in isolated structures which housed these disciplines. This physical isolation is counter to the needs of training in the present era of increasing wealth of medical knowledge; fragmentation and lack of coordination are the

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by-product of isolation. Nevertheless, despite the crumbling of boundaries between disciplines and of departmental barriers, some still cling to the isolated-discipline, pavilion-type concept of health campus planning.

The integration of research with teaching and with health care makes the isolation of facilities for these areas of activity unrealistic and wasteful of time. Architects must become acutely aware of the need for rapid growth of the manpower for health. The U.S.A. is said to face a shortage of 100,000 physicians by 1975. Nursing personnel too is only at about 50 percent demand and no short-term solution is expected. These facts require *a physical plant which will avoid waste of time by health-care personnel* by reducing physical distances traveled to a minimum.

Physical separation is a major obstacle to integration of health-care service. It blocks the achievements possible in the coordination of skills of the health-team. Frequent contact between teachers, students, researchers, and other members of the health-team promotes ideas; when such contact becomes too time consuming it will be episodic, erratic, and less fruitful. Most of our medical buildings are not only out of step with medicine; they are also far below the level of contemporary technology. The problems of continuing education and of research, in their relation to patient study and patient care demand the integration of these spheres of activities in a coordinated bio-medical center.

Another basic factor is the much more rapid pace of change and growth of physical facilities. Changes in the internal arrangement of component elements as well as ample space for growth of the overall complex must be part of the basic planning philosophy. Prolongation of the life of the structure, by avoiding the built-in elements of obsolescence, should be met by design of spaces suitable for convertibility for a variety of uses, at a cost which compares favorably with replacement cost. The static concepts of architectural forms and structural systems are incompatible with the dynamism of medicine.

One of the basic needs is large unobstructed space, free of permanent structural supports and utility risers, but with flexibility of load bearing capacity, and with versatility for variation of story heights. Such basic design elements would satisfy the continual ferment of change. This transitory process cannot be met in structures conceived as final architectural statements which, more often than not, are conceived as monuments to some well-meaning endower. Most of our structures do not meet these basic criteria. And when they don't, they are obsolete whether built a century ago or today.

Another basic need is versatility in utilities services, from climate control of the environment to the most sophisticated equipment or research tool. We have to accommodate mazes of duct work, vents, waste lines, steam, gas, oxygen, suction, various kinds of water lines, high and low tension electrical conduits. Currently, these utilities consume about 50 percent of the construction budget and their cost continues to soar. These expensive installations demand frequent access for maintenance, modifications, replacements, and additions. They should not be crammed into the tightest possible spaces, usually above the ceiling line and hugging the underside of the structural slab above. By providing inade-

quate space, we force them into a crazy-quilt pattern of weird configuration, without chance for access with proper tools. This has been done mostly because of false budget concepts. Trouble is inevitable, however, when the first leak occurs or when the first modifications or additions become necessary.

In short, what's wrong with today's medical centers is their failure to provide a physical form for the optimum integration of the men, the disciplines, and all the components that must function together if excellence is to be achieved. Indeed, in many instances the construction thwarts rather than aids realization of the medical center's stated goals. For example, the trinity of teaching, research, and patient care are considered to be so interlocked that to make clear distinctions between them is held a disservice to health process. The typical design plan, however, is to construct three separate buildings—a medical education or basic sciences unit, a clinical sciences unit, and a teaching hospital—and to connect the three buildings (sometimes by interconnecting corridors on all floors but not always so). Such construction tends to fragment. This separation is frequently further compounded by separate buildings for the library, animal quarters, ambulatory clinics, private practice clinics, and other health schools.

The erection of separate facilities separates the Ph.D. from the M.D. and from the patient in opposition to today's emphasis on interdisciplinary teaching in a more integrated basic science and clinical curriculum. The same holds true for the segregation of the freshmen and sophomore medical students with their basic science teachers in a building separated from the clinical arena, and relative isolation of the junior and senior medical students and patients in a hospital building away from easy contact with basic science teachers.

The requirements of a medical center call for a physical plant that is a compact, highly integrated structure providing ready flexibility, expansibility, and ease of movement. A contiguous physical relationship should encompass the teaching, research, and patient care needs for a particular clinical discipline including hospital beds, out-patient clinics, diagnostic laboratory and x-ray services, private practice offices, research laboratories, faculty offices, teaching space, and animal research quarters. Moreover, "Town" must be brought into the medical center, and closer to "Gown," by providing pooled private practice facilities within the structure for the entire clinical faculty, and for adequate post-graduate teaching facilities.

Treatment of Site

One of the most unsightly external aspects of medical centers is the sea of car-tops blighting the grounds around buildings. The auto is a necessary means of travel, but the needed parking space can be within a structure, out of sight, and need not displace landscaping which can give the buildings an intimate connection with life expressed in lawns, flowers, shrubs, and trees. After driving the car into the building at grade, parking can be extended down and/or up, depending on the nature of the soil and the economy of construction costs. In any case, indoor parking has a dual benefit: 1) it avoids the eyesore of exposed cars; and 2) it brings the parked car closer to the internal transportation

hubs, be they stairs, elevators, or escalators. A drive-in medical center is an asset, with esthetic as well as with practical benefits.

External Approaches. It is necessary to provide for at least four separate approaches: 1) for pedestrians who might circulate via landscaped promenades, between buildings surrounding the medical center, and the center itself; this permits outdoor recreation and relaxed strolling unencumbered by extraneous or dangerous traffic; 2) roads for passenger vehicles for bringing and taking away staff, patients, visitors, personnel, business people to and from the centers; 3) road branches for emergency vehicles and ambulances; 4) road branches for service vehicles making deliveries and removals. The paths of the service vehicles should branch off from the paths of non-service vehicles and should lead independently to delivery and discharge docks; the latter should be, preferably, out of sight of all other traffic patterns.

Basic Organization of Component Elements. There are many ways of relating elements to each other. One is the traditional but obsolete allocation of separate buildings to individual disciplines. It has been rightly claimed (1) that functional development and design which erase the difference between the medical school and the patient-care areas may contribute to the philosophy of unity with meaningful educational relationships. "Supporting patient services such as radiology should be planned in such a way that by appropriate decentralization of select facilities the patients' needs are better served—this is in direct contrast to the conventional, highly concentrated agglutination of facilities which may be slanted toward faculty-staff convenience" (1).

There are three main approaches to the organization of the triad of teaching, patient care, and research: 1) the traditional, but obsolete, allocation of separated buildings to individual disciplines, still practiced abroad as well as on this continent; 2) the still common allocation of a separate building for teaching, another for patient care, and a third for research, these three being sometimes connected at one or more levels; 3) the welding together of all three elements into a single structure in which the triad is still identifiable in separate wings.

None of these plan arrangements truly reflects the interdisciplinary nature of the life sciences. A structure in which teaching, patient care, and research are placed not only in vertical but also in horizontal contiguity comes closest to fostering the team concept made mandatory by the interdisciplinary nature of biological sciences. For instance, the clinical faculty, together with their offices and examination rooms in which they can see in-patients and out-patients, in-patient nursing units, laboratories for clinical diagnosis, diagnostic tools such as x-ray, isotope scanners, EEG, etc., student laboratories in which they can work on experiments, faculty research laboratories, as well as animal rooms should be in as close as possible physical contiguity. This calls for considerable depth of floor space, now made possible by the developing technology which enables us to achieve satisfactory climate control, with proper isolation of odors and infectious materials. Thus, an achievable contiguity can provide the milieu for an effortless intermingling on a horizontal level; moreover, adequate and

well placed elevators and escalators can provide almost as easy contiguity from floor to floor.

The space needs of a bio-medical center are enormous in terms of square footage; they are often in excess of a million square feet, or tens of acres; this calls for structures of considerable horizontal as well as vertical dimensions. Time consumed in horizontal walking plus the time required for vertical travel have to be carefully evaluated before determining a reasonable maximum footage per floor as well as the number of superimposed stories.

Horizontal Groupings. A multi-story structure is almost inevitable. Hence it is essential to scrutinize which of the teaching, patient care, and research facilities are most beneficially arranged in a horizontal relationship and which can function almost as well in a vertical stacking pattern.

There are unquestionably physical relationships of space which can either thwart or benefit patient care. For instance, emergency treatment, some surgery, intensive care, postoperative recovery, clinical laboratories, anesthesiology, diagnostic radiology, isotope scanning, dialysis, inhalation therapy, and pharmacy-sterile supply, when placed in time-saving contiguity, can save lives. This is so not only because mere seconds count in many emergency situations, but also because this juxtaposition of related departments brings the surgeon, the cardiologist, the anesthetist, the nephrologist, the pulmonary specialist, the inhalation therapist, as well as nurses and others together into a team effort when this is a matter of life or death. Moreover, the concentration of life-saving equipment makes its instant availability a further asset to good patient care. Since emergency treatment should be available as quickly as possible, the above mentioned group of services should be readily accessible from the outside of the medical center.

Another important service function which belongs at the junction of the medical center with the outside world is a comprehensive information center; this can now be electronically linked with all sources of information so that instant and correct information can be dispensed at this point. Out of this central information center should radiate conspicuous directional signs leading to the miscellaneous means of access to the desired points of destination. These directional signs should be of proper dimensions for even the weakest of eyesights; strongly differentiated color-coding of signs, corridors, elevator doors, and escalators should lead to the points of destination. One should have no occasion "to get lost" as is so frequently the case in large complexes, especially in round or polygonal structures where points of reference for easy orientation are sorely missing.

Still another desirable and clinically advantageous grouping is the juxtaposition of the department of orthopedics with that of physical medicine and rehabilitation. In addition to patients with orthopedic disorders, all traumatic and other disabled cases benefit from contiguity with staff and facilities of physical medicine and rehabilitation from the standpoint of continuity of care. This proximity is still further enhanced when the laboratory of clinical

pathology and other diagnostic and therapeutic suites, as well as research and teaching for these specialties are placed alongside.

The clinical care of urological and dermatological patients can benefit from contiguity with each other as well as with teaching and research related closely to these disciplines. This applies also to the grouping of ophthalmology with otolaryngology. Psychiatry, neurology and neurosurgery can facilitate better patient care if related physically to each other. This also applies to the grouping of obstetrics with gynecology, and pediatrics with medicine. In all of the above groupings, out-patient examination and treatment may well be jointly utilized with in-patients.

Currently, these groupings have validity; however, with new developments in medicine, initial commitments of location and space may become obsolete long before the useful life of the structure has expired. Under these circumstances, for a structure to be viable, it must have built-in versatility for functional deployment as well as for convertibility and growth.

A New Concept

This writer developed one of several possible new concepts which meet these criteria, while, at the same time, creating the possibility of stimulating esthetic results. In this concept, a series of hollow shafts surrounds an unobstructed floor area of predetermined length and width, the dimensions of which are limited primarily by code regulations governing maximum distance between exits (Fig. 1).

The enclosure of these shafts constitutes the structural supports for the building and its unobstructed floors. Elevators, stairs, ducts, and vertical utility risers are to be housed within these shafts. The floors are all of the "sandwich type;" the upper layer of each "sandwich" consists of a structural framing system having clear-span trusses, with slabs at top and bottom chords. The truss space, by virtue of long spans, is high enough to allow walk-in access to all of the horizontal distribution elements of all utilities and air ducts which will be housed within it (Fig. 2).

The lower layer of the sandwich is a completely unobstructed floor area for the use of occupants of the structure. Any equipment item on the floor can be serviced by utilities above and/or below it, and will be just as easily removable whenever the equipment itself will have to be replaced. Thus, unlimited flexibility of the space can be indefinitely maintained. The vertical shafts and the horizontal truss spaces can be designed for growth of utilities by several hundred or even several thousand percent at relatively little extra initial cost.

The assembly of the vertical shafts with the surrounded horizontal floor sandwiches constitutes an open cagework in which the empty spaces can be initially fully or partially utilized for any desired function. This concept permits varying the square footage encumbered at each floor level, and allows for growth at each level, independent of any other level. Thus, the need for building from the

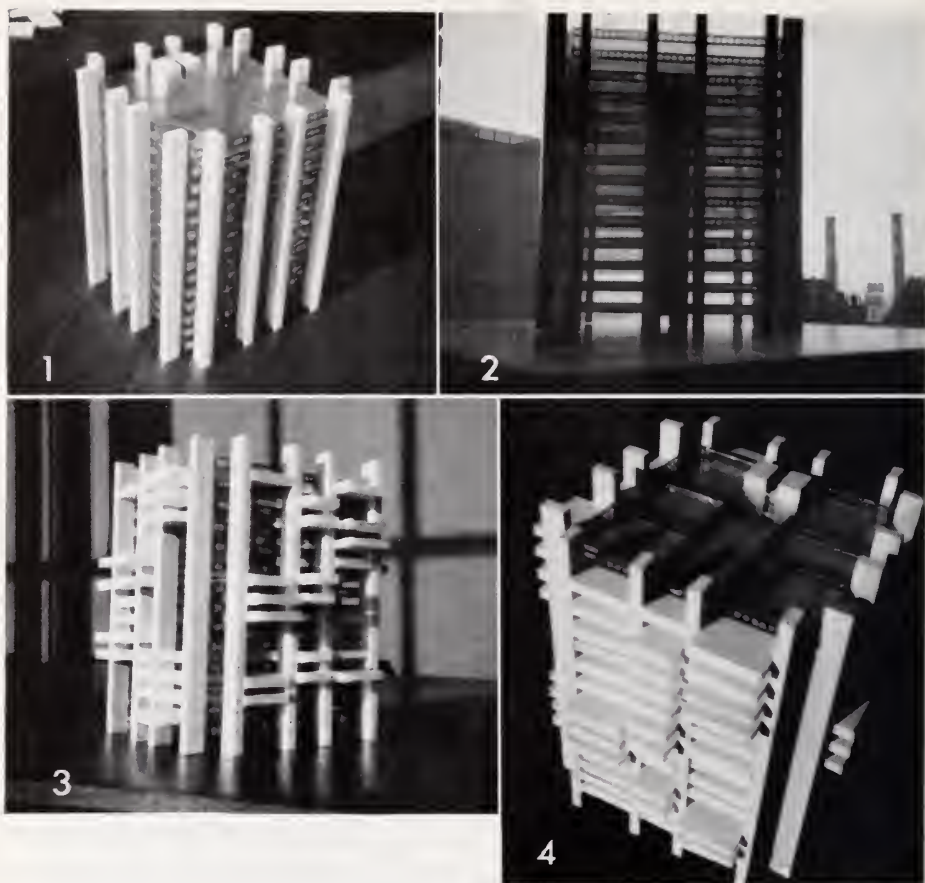


FIGURE 1—4.

ground up every time an increment in an upper story becomes necessary is avoided (Fig. 3, 4).

This concept has other advantages over conventional building concepts: a) In addition to growth possibilities within the cage, contiguous structures of similar or different configuration can be erected alongside, with points of overlap, thus allowing for continuity of circulation between them; b) the versatility of and accessibility to use-space and utilities do away with the need for initial long-term commitment of any functional component. Shifting of departments, in toto or in parts, to any level or part of the structure will be relatively easy and inexpensive.

This is one example of allowance for versatility and growth which can defer obsolescence, which will permit adjustments in functional arrangements and relationships, and yet offers opportunities for imaginative design esthetics; for, within the framework of undifferentiated space it is possible to develop an in-

finite variety of shapes and materials and give due consideration to social, cultural, as well as physical needs of occupants and visitors.

CONCLUSION

Most architects have shied away from revolutionary approaches because of the stringency of unrealistic and miserly capital budgets. If they are to discharge their obligation to society they must raise their sights to the potentials of the scientific and medical revolution. Architecturally viable bio-medical centers need not remain an idle dream. Their realization is well within the capability of our affluent society, with its unprecedented value of the annual gross national product. When fund allocations for health will become adequate, contemporary architecture will be enabled to rise to the challenges posed by the revolutionary march of medicine and will more aptly fulfill the functional as well as the cultural needs of society.

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THE STUDENT

Student Revolt and Our Medical Schools

Charles S. Davidson, M.D.

A medical school without students is not to be conceived as possible, yet the impression sometimes is strong that one's colleagues and even one's self wish the students were in Timbuktu. The extraordinary amount of money both government and private agencies have put into medical research since World War II is at least one well-recognized cause for the diminished emphasis on teaching. Patient care may also have suffered. Although it has undoubtedly been superb in our best "teaching" hospitals, the extension to the community of physicians and health-care personnel has often been slow or lacking. Change in both teaching and patient care is clearly upon us.

The demand of society for medical care (1) and the decreased emphasis of government in pure research (like it or not) will surely make the teaching of medical students more likely to be supported. In addition, and perhaps even more important, today's students are not likely to sit quietly by and be taught, if what is happening in our colleges is any indication (2). Moreover, many students are interested in the social and economic problems of medical care, an interest which probably stems from the same movement the colleges are observing. The purpose of this essay is to enlarge upon these thoughts and to note some of their implications. It is my opinion that established schools need to look carefully at their students, their previous training and experience, but particularly at their motivation and how they see the world. Modifications of curricula will clearly be needed. Schools not yet established, whose curricula are not yet ossified and seemingly immutable, will have an easier task. It is to be hoped that they will take advantage of the changes in students and design their curricula accordingly. Let us take a look at some of the characteristics of today's students which make these changes needed.

One thing is clear, although perhaps insufficiently recognized. Students are today far better prepared than before for college and graduate education. The evidence for this has been well discussed by Funkenstein (3). Education in the sciences continues to improve rapidly. The rate of improvement varies greatly from institution to institution leading to greater diversity in preparation than before (to be discussed later), but the mean is clearly progressively changing toward better science training. Apart from specifically scientific studies, education is generally far better now than even a few generations ago. Students are better informed in many fields. Thus, in planning a new medical school curriculum, the fact that entering students are better educated than before must be considered.

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Because of the diverse kinds of secondary and college education leading to medical school, students increasingly will have had different courses of study. This diversity in kind of preparation must also be taken into account. Thus, students should not be required to repeat in medical school material already mastered in college; they will only be stimulated to learn if they can move ahead. Nothing is so boring as *unnecessary* repetition. Allowing students to move ahead depending on their previous training immediately poses grave problems with the curriculum.

Heretofore, the medical school curriculum was problem enough with departmental pressures assuring that all students were required to take nearly all courses. Can we really modify the curriculum sufficiently to take advantage of the diversity of student preparation and also the diversity of their developing abilities and interests? This will pose a severe test to planners, but already changes of this kind may be seen. A student well trained in college in statistical methods may not be required to repeat this in medical school. Nor is a student who majored in biochemistry in college always put with medical school classmates to whom biochemistry is almost new. To allow these and many more similar possibilities will require considerably more freedom in the curriculum than usually exists now. Funkenstein (3) has suggested that as there are already clearly different "tracks" followed by students in secondary and in college education, so also in medical education a number of "tracks" should be available to take advantage of students' diversity in training and ability. Thus a student whose training in college centered in the humanities, not science, might have a very different "track" from one who entered medical school with high science training, interest, and motivation. Both may ultimately contribute as much to society, but perhaps in different fields.

This concept that some freedom of choice as to courses to be offered the medical student is, of course, not new. Many schools offer elective periods of varying length and freedom. It was President Eliot who upset the Harvard faculty a good many years ago by suggesting that the medical school offer such a multitude of courses that if a student should take each one, it might take his lifetime. To put more freedom of choice in effect, however, will be difficult because someone must decide what is to be omitted. No one wants courses in his specialty to be dropped or even made elective!

The next consideration about our students relates to the current revolution among students which is occurring in our colleges (2) and is already being felt in medical schools. The objective evidence of this revolution is not always happy, at least to us oldsters. One example was the Freedom of Speech Movement in Berkeley. Few campuses have been without some organized protest, although the large state universities have seen the most (4).

These evidences of unrest among college students have been de-emphasized by those who note that college undergraduates always have groups of "radicals" among them and that the present groups come from but a small minority of the student body. Both statements are correct as far as protest is concerned, yet it seems evident to me that these small, vocal, organized groups of radicals

are the "visible" part of a huge iceberg of change in students' attitudes. Many have attempted to analyze this movement (2, 5, 6) and to determine its true background and meaning. It certainly is not communistic (although advantage of some protests have been taken by avowed communists). Moreover, the movement is opposed to the increasing governmental paternalism and bureaucracy of present day life. It stresses the needs of the individual to live and to express himself. In fact, it resembles that old-fashioned American ideal which stood for the individual and his right to control his government and the less the government controlled him, the better. Whatever the circumstances which led to these evidences of revolt among students, the results are becoming evident:

First, students want much more active participation in curriculum planning, methods of teaching, and even choice of teachers than they have customarily had. Some few radicals desire a voice in controlling university policy. It seems reasonable to expect this desire of students to "call the shots" on their teaching and teachers to become evident in the medical schools soon. In fact, last year a small group of students at Harvard, finding some courses not entirely to their liking, petitioned the Dean to allow them to study as they saw fit (7). The request was wisely understood and acceded to. In planning a new medical school, it would seem to me wise to make provision for active and continuing participation of students in curriculum deliberations and even in policy planning.

Second, college students today are much better informed about the world and its problems. Many not only recognize the injustices around them in the form of poverty, racism, and war and the difference between these facts of life and the American ideal, but they also want something done about these matters, not by government, nor at sometime in the future but by all of us and now (2)! Of course, many degrees of urgency are expressed, but the impression is strong that most students are tired of promises, sick of bureaucracy, and anxious to see society take advantage of its opportunities for a better world. Health and the social and economic problems of medical care are among the concerns of these students and this concern is already being felt among students in medical schools. Harvard Medical School, for example, has an active "Medical Care Club." Moreover, among the rank and file of students whom I see, many more than before are interested in these aspects of medicine. Many question what the members of the faculty are doing about these social problems and are openly critical of the extent to which research activities detract from providing medical care as well as from teaching. How long this change will last is, of course, anyone's guess, but it seems to have the characteristics of a solidly based movement. Thus Blair R. Behringer, president of the Student American Medical Association addressing his elders said, in part: "Gentlemen, the medical student of today is in general better educated, better informed on the issues of the day, more concerned about the future of medical practice in this country, and more inclined to do something about it, than you were when you were in medical school."

If this movement is genuine and lasting, and I believe it to be, medical

schools should plan in their teaching far more than before about the facts and problems relating to medicine in the community. It is no longer sufficient for students to learn only in the "teaching hospital" and only from research-minded professors. They want to know about the community around them and what their professors are doing about community health problems. Some medical schools of course have had community health and medical care programs for years, but all too often they have been relegated to second place by faculty and by students. The students are changing. Will the faculty do so? Now that Federal Government support is available more programs of this kind can be expected. Many students will want to take an active part in them. It is my impression that today's more mature student is better prepared for work in the community than before and actively desires it.

Third, today's medical student more than ever seems to be what we all hope for, a mature scholar who wants not only to skim the surface of the great and growing body of medical knowledge, but desires considerable time set aside for him to dig deeply into some subject or concept which interests him. This is a heartening change, if it is a true one, and I believe it is (to a varying degree, of course). This is the kind of intellectual activity which makes true scholarship attractive and productive. To provide more freedom in choosing courses and more time for true scholarship as opposed to superficial, factual learning will come hard in many if not all medical schools. The huge body of medical knowledge and the urgent desire most of us have to teach it and teach all of it are among the many factors which slow down change. I believe future students will expect this freedom and will demand it. Those planning new medical schools have a great advantage in this regard.

Finally, with all this unrest, curriculum upset, community involvement, and freedom of choice for the student to dig deep into a subject, we must pay strict and careful attention to the product of our medical education, the doctor of medicine. Will our new medical student fulfill the needs and demands of society? More important, is scholarship what society wants and needs or should not the physician be more of a technician? The rapid movement into medicine of many new procedures, mechanical and electronic devices, biochemical, biophysical, and bioengineering techniques makes urgent demands on all of us and upon our students to acquire technical expertness. Moreover, the great need for "general practitioners" in the community is real and urgent. Will our future scholar be able to do "general practice?" The answers to these questions are not easily available—if at all.

Some of the technical matters are as well or much better handled by others than by doctors of medicine. Thus, for example, although a physician must have ultimate control, intensive care units are better operated by a corps of highly trained nurses, technicians, electronics experts than by a corps of physicians without specific training and who might be called elsewhere at any time. Much community health work can be done by nurses, social workers, nutritionists, and similar highly trained persons, involving the doctor of medicine only when needed.

If it becomes possible to educate a group of scholars who deserve the medical degree because of their scholarship, not because of their expertness in technical matters, and if other professions and technicians fill the gap, we will be a step nearer to our medical schools being parts of universities rather than technical schools. We shall, in this way, furnish to the community physicians who are capable of organizing and leading that highly complex phenomenon involving much machinery and many people for health or medical care. It will also be the physician's responsibility as the leader of this team to see that the care is not only technically excellent, but continues to "care for the patient" in the best sense of that phrase (8).

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A Student's View

Sidney R. Block

In 1879 Dr. Henry W. Acland of Oxford wrote to the trustees of the newly established Johns Hopkins Hospital and University:

For the complete training of a scientific medical man, three distinct qualities of mind are needed:

- (a). Those fostered by general literary culture.
- (b). Those dependent on special scientific attainments.
- (c). Those which come from close observation of the living sick, followed by, or accompanied with investigation of the dead.

Each of these bundles of qualities is to be fostered, speaking generally, at a special period of life, by a special course of study, and with special opportunities.

They may, taken roughly, be called the School, the University, and the Hospital periods. . . .¹

Today these "periods" are the basis for the course of medical education in the United States. I would like to present, from the viewpoint of a senior student, a few observations and opinions regarding these stages.

Pre-Medicine—"The School"

In general, the premedical student sacrifices an education in the humanities to an overindulgence in the sciences. Afraid of how the medical school admission committees might judge his scientific background, the student takes many science courses in undergraduate school which are to be repeated in the first year of medical school. That the result of this circumscribed education is the "illiterate medical student" is well known, and is often belatedly regretted by the student himself. Once the undergraduate has completed the minimal science requirements for medical school, perhaps with the few extra courses needed to confirm his interest in a medical career, he should be encouraged to intensify his studies in the humanities. Philosophic, literary, historical, artistic thought—all are necessary for an understanding of the human mind with which the doctor must deal, and for increasing his own appreciation and enjoyment of life. Medicine must remain the meeting ground of the humanities and the sciences.

Of Getting In, And Staying In. Medical schools have a responsibility to their students (if not to themselves) to enroll only those students who are expected to be able to satisfactorily complete the course of studies. (And considering the increasing need for physicians in the United States today, one would expect there to be a place in a medical school for every qualified applicant.) The story is told of the professor who addressed the entering medical school class by asking each freshman to look at the student sitting to his right, and the one to his left, and then assured them that at the end of the year one

Class of 1967, The Johns Hopkins School of Medicine, Baltimore, Maryland.

¹ Acland, Henry W., From a letter addressed to Francis T. King and Daniel Coit Gilman, dated Baltimore, September 27, 1879 and reprinted with the first catalogue of the Johns Hopkins Hospital and University, 1879.

of these two persons would not be there! Although medical school cannot but ask for its students' best and consistently best efforts, planned attrition is unnecessary. How much more pleasant and actually more conducive to learning is the intellectual competition between students who realize they all will graduate than the "cut-throat" attitudes of students anxious as to the future.

Grades should be de-emphasized and perhaps not even available to the student body. Written examinations should come infrequently. Since so much of medicine is concerned with personal relationships, ample opportunity for close student-instructor relationships must be provided and the accumulation of instructor opinions through medical school carefully considered in the final evaluation of the student. Cramming for frequent minor examinations and grades results in transient learning and fast forgetting. A more consistently high level of study and indelibility of learning are obtained when the stress is on learning for the sake of increasing one's knowledge; by means of such an approach the student will be impressed with his constant responsibility to his patients to continue the pursuit of knowledge for the rest of his life.

Upon entering medical school the freshman will probably be faced with an alien and anxiety-producing situation—that of not being able to master completely a given subject. For the first time the former premedical student, an intelligent and compulsive person, will have real doubt as to the adequacy of his fund of knowledge in any given course. Beginning the first year medical courses he will again attempt to "learn it all" as he did in college. Anatomy is usually the neophyte's initiation, which some do not survive—not because of any lack of intelligence, but because they are overwhelmed by what they think they have to know, and because they cannot become organized or selective. It is my opinion that the student learns more when he is not overwhelmed, and that the same amount of subject matter can be presented in the same way, and learned just as well, if the student is made to understand from the beginning that he will be unable to master thoroughly any given subject and indeed is not expected to do so. He should be made to know that there is a relative importance to the facts he is trying to learn and that the more he does assimilate the better off he will be; but that what is truly important and expected of him is an *understanding* of all he reads and observes. From then on, constant repetition throughout the school years will finish the job.

For example: almost all medical students need a mnemonic when first learning the cranial nerves; but two years later, after repetition and constant use, it is more difficult to remember the mnemonic than the nerves themselves. It is recommended that the student choose the most complete textbook that he is able to read in the time allotted. The "definitive" text is detailed and explicative so that the material may be understood; and it is reiterative enough so that, while reading solely for understanding, the student will learn more than if he tried to commit to memory the information available in an abridged review book. Lecture notes and outline books which keynote the important facts can be helpful when used to review for examinations. An increased use of visual aids is also recommended—charts, models, and motion pictures create lasting impressions by pictorializing reading and clinical material.

The Basic Sciences—"The University"

The courses of the two basic science years should be studied separately, but at the same time they should be related to each other and the clinical courses, and given in a specific logical order. Thus the student learns what exists (anatomy and biochemistry), how it normally functions (physiology), what can go wrong (pathology and microbiology), and in the last two years, how to diagnose the illness (third year) and how to treat it (fourth year). The order is important—one cannot study urinary function until he knows the anatomy and histology of the kidney. Some educators prefer to schedule basic science courses concurrently, but I feel that it is easier to study in its entirety one subject at a time. Each subsequent course then forces the student to review, interrelate, and integrate all of the previous courses. It is this repetition which is most effective in learning.

On the other hand the student must not be left to himself to form this integration. Many times the student fails to see the relevance of the basic sciences to each other and to his goal in clinical medicine. The courses of the basic sciences are studied as islands of knowledge and the student is left to swim from one to the other. Perhaps, at least in part, the basic sciences should be taught by clinicians who can build bridges between these islands and to the continent of clinical material.

Whether researchers or practitioners are the best instructors is an unnecessary controversial issue. The best teacher, be he practitioner or research specialist, is the one who can impart his knowledge and experience so that it seems important, interesting, relevant, and can be incorporated by the student. The researcher who does not have the ability or the desire to teach should not be asked to do so; the practitioner who can adequately keep abreast of developments and who has the ability and desire should be utilized. To improve the quality of instruction medical school professors might profit by taking a few basic courses in the philosophy and practice of education. Students should be asked to evaluate the clarity of instruction at regular intervals.

More than ample reason exists for exposure to research techniques in the basic sciences and this should be done at the expense of the old-fashioned cookbook-type laboratories in which the student participated in undergraduate school. Principles of "classic" experiments can be presented in the form of demonstrations. I was exposed to supervised small group projects designed to answer a specific question in a matter of a few months part-time effort. I remember not really enjoying them at the time; the questions seemed trivial and irrelevant and more often than not went unanswered. In retrospect (and perhaps students should be made to understand this in a prospective sense) I realize that, although the questions were of little importance, the ultimate purpose was to discipline the mind by utilizing a new method in the approach to and the solution of problems—a sound teaching procedure.

In order to balance the emphasis on science which takes place during the "University period," the student should be made more aware of the psychology, philosophy, and history of medicine.

The Clinical Years—"The Hospital"

The clinical years take the student out of the classroom and put him in intimate contact with patients on the wards. It would seem best to separate these two years; the first emphasizing diagnosis, the second therapeutics. Again, repetition is the keynote. By now the student has become accustomed to approaching and incorporating new disciplines; however, in many ways the clinical studies are so different that they warrant another orientation and further organization of the student's mind. The introduction to a new disease should be dogmatic via the "classical case," but the student should learn not to be dogmatic when it comes to the individual patient. He must be made to understand that in a given situation the particular manifestations of any disease may be atypical.

The student must learn to be critical and to modify his "book learning" with his own experience; he should begin to learn how to educate himself. As one of my professors once said, "Fifty percent of what we teach will prove to be wrong . . . only we don't know which fifty percent it is!" Of prime consideration, here, is the personal library of basic texts in all fields (another reason for accumulating definitive texts in each course) and selected journals in the field of special interest. For the student entering academic medicine an article file or card index to his journals might be started. The practitioner, in general, will read both for interest and the need to keep up with medical progress. Differentiating between "medica trivialis" or "acta inconsequentia" and the well-structured meaningful study is an art which professors should try to impart to their students.

The two years of the "Hospital period" is a short time when one considers the basic knowledge and techniques the student hopes to assimilate. Most of the student's time is spent with patients, but there must also be adequate time for reading. Clinical research and specialty electives should be made available and encouraged. However, it is unwise to place pressure upon the student at an early stage to choose a field of medicine in which to specialize. Though fortunately most students are able to do this on their own, and can then spend elective time concentrating in a specialized area, there should be a reasonable period of time for undecided students to examine the different medical fields. By the same token I would not agree that, once a student chooses a field of interest, he should abandon study in all other areas. Persons in one specialty must be exposed to and have respect for the abilities, limitations, and philosophy of the other specialities.

The student's time is far too important to be wasted on unnecessary laboratory ("scut") work. Though he should know how to do routine tests and procedures, and be able to evaluate the results and limitations, he should be required to do only the admission laboratory work and thereafter observe the final phases of future studies.

The student should have reasonable responsibilities for his patients so that he may gain self reliance. He must be aggressive in learning procedures. "See one, do one, teach one" is approximately the right approach for learning such

procedures as bone marrow aspirations, lumbar punctures, suturing, thoracenteses, etc., which should be a part of his repertoire before graduating.

The medical student must be an integral part of the hospital and the hospital should be oriented towards him. Besides learning, the student has a role in hospital life. Because he is rather unbiased towards conflicting ideas and uncolored by personal experience, he must be encouraged to speak up and question what he sees and hears. Thus he will not only increase his own understanding, but he will also stimulate his elders to review and question their own concepts.

CONCLUSION

The medical student does not expect or wish for an education obtained without effort. He does wish to have the opportunity to obtain the fund of knowledge and experience commensurate with his responsibilities and obligations upon graduation. Perhaps these suggestions will aid in the attainment of this goal.

PROPOSED CURRICULUM FOR THE MOUNT SINAI SCHOOL OF MEDICINE*

Tibor Barka, M.D.*; George Christakis, M.D.†; Howard L. Gadboys, M.D.‡; David Koffler, M.D.§; and Fenton Schaffner, M.D.||

The formulation of the curriculum presented herein followed the study of the educational philosophy and curricula of several existing and developing American medical schools. These curricula are of three major types: 1. classical teaching as initiated by the Flexner report (1); 2. integration of basic science subjects as exemplified by the curriculum developed by the Western Reserve School of Medicine (2); 3. yearly alteration of basic science and clinical medicine at Duke University School of Medicine (3). Several aspects of these curricula were considered including the number of hours allocated to each subject, the degree of integration among disciplines, new subject matter, the time and mode of introduction of the student to the patient and clinical medicine, and the role of behavioral and social sciences in medical school teaching.

The proposed curriculum takes into consideration the past excellence of Mount Sinai Hospital in patient care, clinical teaching and research, the recent trends in medical education, and the future needs of society. It is based on the curriculum submitted to the Association of American Medical Colleges and approved for the Mount Sinai School of Medicine (4). The basic philosophy of the curriculum encompasses the Mount Sinai Concept (5) which balances three objectives in the training of the future physician, namely: 1. introduction of quantitative biology into medicine with inherent area-specialization; 2. counteraction of the depersonalization of the organ-specialized physician by the broadening influence of social sciences and human studies; 3. provision of good care for every patient beginning with the presymptomatic stage, the aim of community medicine.

First and Second Year Curriculum (Table 1)

Organization of Teaching. The teaching time is distributed by trimesters for each of the four years.¶ The first trimester of the first year is devoted to de-

* This represents the proposal of a curriculum strongly endorsed by the editor, but not yet accepted as policy by the school. The Editor.

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¶ A cumulative trimester system is used throughout this article and the entire four year period is viewed as a series of trimesters.

partmental instruction in the fundamentals of basic science. During the second, third and part of the fourth trimesters, an integrated curriculum on the normal and abnormal structure and function of the various organ systems will be presented. Concurrently, clinical medicine, including behavioral science, community medicine, philosophy, and jurisprudence will be introduced in a course designated as "Introduction to Medical Care." In the fifth and sixth trimesters, the teaching will be organized according to pathophysiological principles of disease processes. This method introduces the student early to the complexity of medical science in a stepwise fashion with recall of material previously studied, but now placed in a different perspective.

Table I describes the distribution of block time for anatomy, biochemistry, pharmacology, physiology, pathology, and microbiology. It also shows a suggested time distribution for each organ system and subject area. The block time in each subject area will be organized at the discretion of each department. The basic principles of the various subjects will be presented during this period. It is suggested that gross anatomy and dissection be included in the section for anatomy. In other areas, general principles which will serve as the basis for the teaching of each subject area in the integrated curriculum should be covered during the period of the block time. In contrast to the block time, the organization of the teaching on organ systems and pathophysiological processes will be the responsibility of the subject committees. A representative of each department pertaining to the particular area as designated by the Chairman, will be a member of the subject committee. The curriculum coordinator will serve as the liaison between various subject committees and help to correlate the teaching in subject areas. In most subject areas, each department will participate in the integrated teaching program. In some areas, one department will predominate over all others. The following is a list of the major departments involved in each subject area:

Blood: pathology, physiology, and biochemistry.

Cardiovascular System: physiology, pathology and pharmacology.

Gastrointestinal System: physiology, pathology, microbiology and biochemistry.

Liver, Pancreas and Biliary Tract: biochemistry, pathology, physiology and pharmacology.

Respiratory Tract: microbiology, physiology, biochemistry, and pathology.

Kidney and Genitourinary System: biochemistry, physiology, microbiology, and pathology.

Reproduction: pathology, physiology, and microbiology.

Musculoskeletal System: biochemistry and physiology.

Central Nervous System: anatomy (neuroanatomy), biochemistry, physiology, and pathology.

Endocrinology: physiology and biochemistry.

Growth and Development: anatomy (embryology) and pathology.

Infectious Disease: microbiology, pathology, and pharmacology.

Immunology: predominantly microbiology.

Oncology: predominantly pathology and biochemistry.

Degenerative Disease: predominantly pathology and microbiology.

Environmental and Toxic: microbiology and pathology.

Elective Time (Free Curriculum). During the elective time the student will, in principle, be considered as a graduate student. This implies that every attempt will be made to fully utilize his time under close guidance of the faculty. The free curriculum serves three purposes:

To provide study in depth in one area. This need not necessarily be related to the final area of endeavor of the physician, but may, for instance, give exposure to laboratory and research type activity for the student who eventually may enter a nonacademic type of practice; a future laboratory physician may temporarily be exposed to illustrative work at the bedside.

Concentrated work in one area may give the student the early opportunity to test his career objectives, motivation, and ability in a given area of medicine. This might result in desirable early reconsideration of his primary field of interest.

This activity may be more helpful in the evaluation and guidance of the student, e.g., as to type of internship or of other postgraduate work, than classification by grades or examinations as the sole criterion. If the student understands that his activities in the elective time component of the curriculum will be a key element in evaluation, he will be motivated to put more effort into his elective activities than is usual in other schools.

Three principal areas are contemplated: (A) laboratory, (B) clinical, and (C) sociological.

(A) For laboratory activity the student will be assigned, according to his own choice, to one specific laboratory and to one faculty member (sponsor) with whom he should work, either participating in his sponsor's activities or carrying out a related project under the sponsor's supervision. Research achievements will not be the primary purpose of these laboratory activities, but rather exposure to the thinking of an investigator including familiarity with experimental strategy and appreciation of quantitation.

(B) In clinical activity the student will work as a clerk on an in-hospital service or an out-patient clinic, dealing usually with a specialized field. Again, for this purpose, he will be assigned to one sponsor whom he might accompany, in apprentice fashion at all his clinical activities.

(C) The student may be concerned with out-patient clinics dealing with primarily social, ecologic or comprehensive medical care activities, or with specific social work problems (for instance, alcohol, birth control clinics, or behavioral and anthropologic agencies). Again, an attempt should be made to assign him to one sponsor.

A list will be available from which the student could choose the activities available in these three areas in the medical and graduate school.

These three types of activities should be, but need not be supplemented by participation of the student in various seminars of the medical school and particularly of the graduate school. One of the seminars should be related, if possi-

ble, to the main line of his endeavor at that given time in the free curriculum. He should, furthermore, be encouraged to participate in a second seminar unrelated to the field in which he is working. It might, at times, be decided that the student does only seminar work in his elective time. One of these seminars would then include laboratory or field work.

Since flexibility is to be the key in the free curriculum, the assignment should be arranged for the student by a faculty advisor or tutor (and members of a free curriculum committee) who consult with the student. This committee is composed of members of the medical school and graduate school who are well informed about the existing academic and research opportunities.

During the four years, an attempt should be made to expose each student to one elective period in one laboratory area, and one in a clinical area. However, he may have several different elective areas during the four years of medical school depending upon his own desire and the guidance provided by his advisor and the free curriculum committee. Premature termination of previously chosen assignments should not be encouraged but might be agreed upon at the request of the student or his area sponsor if real incompatibility exists between student and the sponsor or if the student develops strong dislike for the area chosen. Such an agreement should be a combined decision of the advisor with the free curriculum committee.

Role of the Laboratory in Medical Teaching. Modern laboratory methods applied either routinely for diagnostic purposes or in investigation are for the most part automated and generally too complex for student use. Therefore, the process of acquainting students with techniques should be by demonstration rather than by performance of exercises using outmoded methods. For instance, determination of serum albumin by salting out techniques is neither accurate nor of teaching value.

The main purposes of laboratory exercises in the "functional" sciences, i.e., biochemistry and physiology, are recall and reinforcement of learning by other means. This will be enhanced by integrating biochemical and physiological aspects in the individual experiments. The availability of the multi-disciplinary laboratory (6) will make this possible and even beginning in the first trimester a few carefully chosen experiments are planned. Through observation of the effects of cholinesterase poisons, such as difluorophosphate on body function and enzyme activity, as well as on enzyme activity during the recovery phase, the principles of toxicology, neurophysiology, enzyme kinetics and protein synthesis can be demonstrated in a single experiment. Similarly, the effect of injection of laked red cells can illustrate haptoglobin function, synthesis and genetics as well as protein separation by electrophoresis.

By contrast in the "observational" or "morphologic" sciences, i.e., anatomy, pathology, hematology, laboratory tissue is necessary for each student to acquaint himself with qualitative aspects which cannot be well or completely taught by demonstration or projection of slides.

Development of understanding of quantitation and laboratory thinking should be part of experience acquired during elective time, spent in the labora-

tory actually working under an investigator as a member of his research team. Under these circumstances, quantitation acquires its rightful significance.

Thus, during the introductory block time on the first trimester, three or four integrated experiments in fundamentals are planned. In each subject area in the later trimesters, one major experiment should be performed, all as interdisciplinary as possible.

Introduction to Medical Care. While the details of mechanisms, diagnosis and management of specific diseases of the various organ systems will occupy much of the teaching efforts of the integrated program in the clinical, as well as in the preclinical trimesters, the student must also understand the problems of the patient as a whole and those of delivery of medical care (7). This is particularly necessary because many of our students can be expected to obtain further training during the residency years leading to subspecialization. A course entitled "Introduction to Medical Care" is planned:

1. To provide this understanding early in the student's medical school career.
2. To satisfy his clinical interests early.
3. To provide correlation with basic science information.
4. To prepare him for the clinical clerkships in the junior year.

In addition to training in the techniques of clinical medicine, such as history taking and physical diagnosis, this course will include behavioral sciences, community medicine, human ecology, delivery of medical care, and medical ethics. As much as possible, the latter subjects will be dovetailed into the subject areas of the integrated program. While some of this teaching will be of the classroom type and demonstrations, seminars and field trips will be encouraged, much will be focused on individual patients. One to four students will interview or examine a patient and members of his family, seeking out different aspects of his illness. For instance, he may learn: 1. the manifestations of the disease itself, 2. the impact of the disease on the life of the patient and his family, and 3. the interplay between the patient and his environment in relation to the disease. The advantages of using direct contact of students with individual patients are: 1. stimulation of the student's interest by dealing with patients early, 2. reinforcement of the learning processes by the personal concern of the student for the patient's problems, 3. rapport between student and patient, enabling the student to elicit with greater detail and understanding the factors operative in the illness and in the life of the patient. Each student will thus have the responsibility of a detailed analysis of few patients during the course but each patient may serve in several ways. He may be the subject of a discussion 1) on physical diagnosis for a group of students at the bedside in ward-rounds fashion with the responsible student or students demonstrating the findings to the rest of the group, 2) on the disease itself in a subject area where the student will present the history and findings to the entire group, 3) on the behavioral aspects of the disease, the patient or his family, and 4) on the economic, social, ethical, legal and anthropologic factors operative in the case. This in depth pursuit of the social and human details of the life of one person will serve to coun-

teract the depersonalizing effect of specialization to which the student is constantly exposed.

At the same time, the essence of clinical thinking, as well as the principles and practices of medicine, surgery, pediatrics, obstetrics, and psychiatry are instilled in the student as he follows the patient through the episode of illness that brought the patient to the hospital. He will have the opportunity to discuss with his instructors, as well as with the attending and house staffs, the problems of management that arise. Students will thus be prepared for the clinical clerkships, eliminating the need for further introductory block time in the third year.

Finally, this course will provide the opportunity to demonstrate to the student the relevance of basic science knowledge to patient care by correlating the clinical problems with the subjects taught in each phase. For proper evaluation of this proposed course, it must be pointed out that 468 hours are assigned for it during the first two years, and that the course begins with a few hours as an introduction already in the first trimester. During the first trimester one hour each will be devoted to a period of introduction by the internist, surgeon, pediatrician, obstetrician, psychiatrist, community medicine staff member, sociologist, etc. for a total of 12 or 13 hours. It is suggested that about one-third of the total time of the course be devoted to teaching the principles of the major medical specialties (about 40 hours each) one-third to social, behavioral and economic aspects, and the rest be devoted to correlation with basic sciences. The first two are equivalent to block time teaching for each of these clinical specialties. Some opportunity will be available for the students to choose patients with diseases or problems in which they may be interested. Moreover, further exploration by the students into any of the clinical areas during the second year will be encouraged by having limited clerkships available as electives, as well as opportunities to participate in clinical research projects.

Third and Fourth Year Curriculum (Table 2)

The curriculum in the third and fourth year is divided into three segments. The first is two trimesters of 15 weeks each which is modified clinical clerkship. The second also consists of two 15 week trimesters, one trimester devoted to completion of the clinical clerkship and the other to outpatient care. The final segment is made up of two 13-week trimesters devoted fully to electives depending on career goals.

First Segment (Trimesters VII and VIII). Since the student will have been indoctrinated in the principles of history taking, physical diagnosis and the approach to the patient as well as the principles of the various major medical specialties in the Introduction to Medical Care, particularly in the time during the second year when disease processes are taught, no further time is allowed for indoctrination. To permit teaching to small numbers of students, the class initially will be divided into four groups. No elective time is included during these trimesters in order to permit as much time as possible for exposure to practical clinical problems. The curriculum coordinators have attempted to

construct an integrated clerkship to maintain the system of integrated teaching begun in the first two years. The only way this seemed feasible was integration of medicine, surgery, and pediatrics by subject areas. The subjects chosen in the first segment were cardiovascular-renal diseases, gastrointestinal diseases, neurological and muscular diseases, and oncology (Special Medicine and Surgery). The gastroenterology and oncology portions will be predominantly surgical and the cardiology and neurology portions medical. Initially, 4 to 6 students will be in a group. For example, those assigned to surgical gastroenterology (3 to 4 students) will study surgical patients whether adults or children. The same will be true for medical gastroenterology (1 to 2 students). All 4 to 6 students will make rounds together with the surgeons, gastroenterologists, or pediatricians on different days, or with all of these specialists together on appropriate cases.

Within each subject area weekly one hour conferences are suggested in the following: basic sciences, therapeutics, psychiatry, radiology, pathology, and community medicine. This will mean one conference daily with perhaps basic sciences and therapeutics consecutively. These conferences would mainly be of seminar type run by the students with a faculty moderator. These could also include some didactic material but this should be kept to a minimum both for the students and the faculty. Demonstrations, slide projection, and patient presentation can also be included when necessary.

In order to introduce the student firsthand to diagnosis of major psychiatric illness in adults and children, a block of two weeks is set aside for each group in this segment. Conferences will be held during this time as during other subject areas. (Table 2A.)

Second Segment (Trimesters IX and X). Half of the class will spend all of trimester IX in the outpatient clinics and the other half trimester X. Those not in the outpatient clinics will be on the Obstetrical and Gynecology service for six weeks. It is anticipated that each student will spend two weeks on 24 hour call in the delivery room. The remainder of the time should be spent in prenatal clinics, gynecologic diagnostic and tumor clinics, family planning clinics, obstetrical medical and psychiatric clinics, and on gynecological and medical obstetrical ward rounds. Since about 90 percent of our graduates will not call on their own obstetrical knowledge or skills again in their careers, the general diagnostic and medical, surgical, and psychiatric problems should be emphasized. An additional two weeks will be spent in the nurseries to learn of the specific problems of the newborn. The remainder of that trimester will be divided between pulmonary and infectious diseases, the latter mainly spent in pediatrics. Conferences will be the same as those of the preceding two trimesters.

The work in the outpatient clinics falls into nonelective group of assignments and electives, the latter about one-third of the total. The nonelective clinics will include those chronic chiefly medical problems where a longer period of patient observation seems advisable and which generally are managed in ambulatory

patients. These are dermatology, hematology (anemias), arthritis, and diabetes. The elective clinics will be chosen from physical medicine, nutrition, ophthalmology, otolaryngology, endocrinology, orthopedics, urology, psychiatry, or any of the other medical, surgical, or pediatric clinics.

To provide the student with knowledge of some of the problems involved in initial patient-physician contacts and to teach him some of the fundamentals of emergency care, he will spend a half day per week in the emergency room during the entire trimester. In addition, he will attend a general ambulatory care clinic where adults as well as children will be seen for the first time, and then for subsequent follow-ups if the patient is not referred to a specialty clinic.

The number of students assigned to each clinic should be two or three depending on how often the clinic meets. Informal conferences will be held when indicated in each of the clinics. At the completion of the tenth trimester, a comprehensive examination based on clinical medicine will be given. (Table 2B.)

Third Segment (Trimesters XI and XII). The last six months of the student's medical school career should be elective with the choices made according to career goals (Table 3). Sets of electives will be available for those with clearly established career goals. The electives will be balanced mixtures of basic science laboratory work and clinical experience. The effort will be made to provide exposure to areas related to the career goal which will not be readily available during residency training. Thus, the future internist or surgeon might learn details of the effects of alpha and beta adrenergic stimulants and blockers on cardiovascular or gastrointestinal function, structure and function of electronic devices used in medical or surgical monitoring of bodily functions, or general medical or surgical aspects of various subspecialty practices other than those to be pursued later. The sets of electives would be partly prearranged so that balance between disciplines is achieved. A mixture of subjects will be available for those who have not made choices or for the few who want to enter general practice. During this period, a student may spend much of his time in research either participating in an ongoing project or carrying out some independent work which can be done practically and in the limited time available. While this will be greatly encouraged, it cannot be made mandatory for many obvious reasons. No formal written presentation of work performed during this period of time should be required, but this, too, should be encouraged by publication of meritorious works, by prizes, and by honors at graduation. It is expected that all students will have obtained passing scores in the National Board examinations.

Several items in the proposed curriculum for the second two years deserve further comment and explanation. The attempt to integrate the clerkship is to try to give a hitherto formless area of medical education some structure. This will require careful policing by the curriculum coordinator and by subject committees for the specific areas to prevent poor balance of material presented. Since it has become obvious that all of medical knowledge cannot be taught,

but only principles, an attempt will be necessary on the part of the subject committees to see that students are exposed to as many principles as can comfortably fit into the crowded schedule. This will be made easier by virtue of the fact that subject committees will be concerned only with areas of their own interest. Furthermore, the seminars and conferences can be used to fill gaps that occur as a result of imbalanced clinical material.

The integration by subject areas makes for the most efficient utilization of the knowledge of the teaching staff. Objection has been raised to this very point with the claim that the physicians concerned with minutiae in a circumscribed area cannot properly place matters into an overall scheme of things (8). Actually the converse, superficiality in the application of principles, may pose a far greater danger. Furthermore, the extent of integration of separate areas of clinical medicine into a single fabric is determined by individual factors established long before the student enters medical school. In essence, all that can be demonstrated in the clinical years of medical school are the principles of management of episodes of illness and then by extrapolation the management of illnesses in general is taught.

The impact of episodes of illness on the individual, his family and community, as well as the influences of these on the episodes of illness, are areas just now being explored by the medical profession (9, 10). In anticipation that these will be important for the future physician, much emphasis is given them in our curriculum. Thus, while psychiatry is given only a small amount of block time, it is hoped that the major portion of the teaching will be in relation to actual patient problems in the specific disease areas (11).

Finally, a word must be said about the finality or lack thereof of the scheme proposed. One of the duties of the subject committees, particularly the chairmen, is to evaluate the material they present in terms of worthiness of time spent. This will have to also be done independently by the curriculum coordinators and by the departmental chiefs. From such observations changes will come, some in the form of minor adjustments and some as major upheavals. Only by keeping flexibility as the keynote, can our curriculum continue to serve its purpose to always provide for the adequate training of the physician for the years ahead (12).

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TABLE 1.—Distribution of hours during first and second years based on a 40-hour per week (13 week) trimester

	First Year								Second Year						Totals		
	Trimester I	Trimester II				Trimester III				Trimester IV			Trimester V	Trimester VI			
		Blood	Cardiovascular	Respiratory	G.I.	Liver-Pancreas-Biliary	Kidney and Genitourinary	Reproduction	Endocrinology	Musculo-skeletal	Nervous System	Growth and Development	Infectious Disease	Immunology		Oncology	Degenerative Disease
Anatomy (inc. gross dissection & cytology lab)	169	65 hours	65 hours	52 hours	65 hours	39 hours	52 hours	65 hours	52 hours	52 hours	65 hours	65 hours	52 hours	52 hours	65 hours	52 hours	52 hours
Biochemistry	156*																
Pharmacology	26																
Physiology	65*																
Pathology	13																
Microbiology (including lab demonstration)	26																
Totals	455	286				221				182			117		104		1365
Biostatistics and Computer Genetics		26				26									13		52
Introduction to Medicine	13	91				91				91			91		91		13
Elective time	0	65				130				195			260		260		468
Free Time	52	52				52				52			52		52		312
																	3120

* From these a total of 20 hours will be reserved for combined biochemical and physiologic experiments.

Table 2A. Distribution of Subjects in Trimester VII-VIII*

THIRD YEAR							
Trimester VII				Trimester VIII			
Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr
GI		PSYCH	NEURO-MUSC.	CARDIO-VASCULAR		SPEC. MED. & SURGERY	
NEURO-MUSC.	PSYCH	GI		SPEC. MED. & SURG.	CARDIO-VASCULAR		
CARDIO-VASCULAR		SPEC. MED. & SURG.		NEURO-MUSC.	PSYCH	GI	
SPEC. MED. & SURG.		CARDIO-VASCULAR		GI		PSYCH	NEURO-MUSC.

* For the comprehensive subject areas—Gastrointestinal, Neuromuscular, Cardiovascular-Renal, Special Medicine & Surgery (Tumors), and Respiratory-Infectious Disease—the specified number of weeks will be spent in the Medical, Surgical, and Pediatric Services.

This includes 1 hr/wk each in: Basic Science; Therapeutics; Psychiatry; Radiology; Pathological Correlations; Community Medicine and Social Aspects.

Table 2B. Distribution of Subjects in Trimester IX-XII*

THIRD YEAR				FOURTH YEAR				Trimester XI & XII	
Trimester IX				Trimester X					
May	June	July	Aug	Sept	Oct	Nov	Dec	Dec-June	
OPD†				RESP-ID		OB‡		Clinical Electives or Research	
OPD†				OB‡		RESP-ID			
OB‡		RESP-ID		OPD†					
RESP-ID		OB‡		OPD†					

† OPD includes: Ambulatory Care; Emergency Room; Dermatology; Hematology; Arthritis; Diabetes.

The following electives may be offered: Physical Medicine; Ophthalmology; ENT; Nutrition; Endocrinology; Orthopedics, Urology, Psychiatry.

‡ OB includes Neonatology.

TABLE 3

*Illustrative Electives in Trimesters XI and XII (December—June)**Department of Medicine*

Research Problem*	Inborn errors of Metabolism
Biochemistry	Ophthalmology
Community Medicine	Pharmacology & Therapeutics
ENT	Postoperative Management
Immunology	Psychiatry

Department of Surgery

Research Problem*	Pediatrics
Anatomy	Physiology
Bio-Engineering	Psychiatry
Immunology	Radiology
Medicine	Surgical Pathology

Department of Pediatrics

Research Problem*	Nutrition
Biochemistry	Pharmacology
Genetics	Psychiatry
Medicine	Surgery
Neurology	Virology

Department of Obstetrics

Research Problem*	Population Genetics
Anatomy-Embryology	Psychiatry
Endocrinology	Radiology
Medicine	Surgery

Department of Psychiatry

Research Problem*	Neurosurgery
Community Medicine	Pharmacology
Medicine	Surgery

Department of Community Medicine

Research Problem*	Pediatrics
Medicine	Psychiatry

Department of Pathology and Radiology
(Or other laboratory clinics)*Undecided as to career goals*

* It is suggested that students selecting a research problem prepare a project paper or "minor thesis" at conclusion of project.

Research project may be in another institution or abroad.

DISCIPLINES

Physics, Biology and Medicine

Sergei Feitelberg, M.D.

The existence of physics laboratories and physicists in medical schools and academically oriented hospitals at the present time can probably be traced to the suggestion made in 1928 to replace biological methods of measuring x-ray and radium doses (i.e., erythema dose) by a purely physical method based on a clearly defined unit, the roentgen, a suggestion which was internationally accepted in 1937. Precise dosimetry, which had been a special pursuit of a few pioneers, became a required routine procedure in medical practice. In order to make these measurements with the new and unfamiliar instruments, physicists joined the medical staffs, usually as members of radiology departments. A new impulse in this direction was given about 20 years ago, when radioactive isotopes entered the field of clinical medicine and of medical research. The need for physicists or for their assistance continued to grow with the introduction of more and more complex physical instrumentation, with which a biologist or physician was usually unfamiliar (ultracentrifuge, electron microscope, mass spectrometer, etc.). While these rather spectacular developments created a clear and unequivocal need for physicists and their help, the role of the physicist was that of a glorified technician engaged in methodology and instrumentation, dignified only by the strangeness of his doings and the mysteriousness of his tools.

In the present paper, I would like to speak of an entirely different aspect of physics in biology and medicine, namely of the exchange and cross-fertilization of these disciplines on a more conceptual level.

This exchange has existed for a long time and has been fruitful, rather strangely, in the direction from medicine to physics. The geocentric system of astronomy was first proposed by a man of medicine: Copernicus. Perhaps the greatest discovery of physics, after Newton's gravitation theory, was the conservation of energy, formulated clearly by two physicians: Robert Mayer and Hermann von Helmholtz. Why was that a one-way street? I shall not try to solve this puzzle, although it is not quite true that physics, as a natural science, remained remote from life sciences.

Let me try instead to indicate some contributions which physics has made to biology and the directions in which it can still do so. The law of conservation of energy, as it is reflected in the understanding of quantitative aspects of metabolism, is such an integral part of biological thinking that we

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rarely realize that we are employing physics when we watch our calorie intake, or when we consider intricate aspects of muscular or neural activity.

Conservation of energy is usually called the first law of thermodynamics. The biologist and certainly the physician are much less familiar with the second law of thermodynamics, which deals with the concept of entropy and the statement that a system left in isolation tends to increase this quantity. A familiar example or application of this law is the theory that the universe is approaching a "thermal death," a state in which all forms of energy are converted to a uniform level of heat, so that "nothing will be happening anymore." Note the biological term, "death."

The remarkable implication of entropy is that this is the only purely physical concept which predicts the basic direction of events in a system, while "direction" is usually a biological concept. It is probably not an accident that Freud "invented" a death instinct (1), which seems to derive from the entropy concept (2). An impressive presentation of these ideas is to be found in a book by Schrödinger (3), one of the truly great physicists of our time.

It is by avoiding the rapid decay into the inert state of 'equilibrium', that an organism appears so enigmatic; so much so, that from the earliest times of human thought some special non-physical or supernatural force (*vis viva*, *entelechy*) was claimed to be operative in the organism, and in some quarters is still claimed.

How does the living organism avoid decay? The obvious answer is: By eating, drinking, breathing and (in the case of plants) assimilating. The technical term is *metabolism*. The Greek word . . . means change or exchange. Exchange of what? Originally the underlying idea is, no doubt, exchange of material (e.g. the German for metabolism is *Stoffwechsel*.) That the exchange of material should be the essential thing is absurd. Any atom of nitrogen, oxygen, sulphur, etc., is as good as any other of its kind; what could be gained by exchanging them? For a while in the past our curiosity was silenced by being told that we feed upon energy. . . . Needless to say, taken literally, this is just as absurd. For an adult organism the energy content is as stationary as the material content. Since, surely, any calorie is worth as much as any other calorie, one cannot see how a mere exchange could help.

What then is that precious something contained in our food which keeps us from death? That is easily answered. Every process, event, happening—call it what you will; in a word, everything that is going on in Nature means an increase of the entropy of the part of the world where it is going on. Thus a living organism continually increases its entropy—or, as you may say, produces positive entropy—and thus tends to approach the dangerous state of maximum entropy, which is death. It can only keep aloof from it, i.e. alive, by continually drawing from its environment negative entropy—which is something very positive as we shall immediately see. What an organism feeds upon is negative entropy. Or, to put it less paradoxically, the essential thing in metabolism is that the organism succeeds in freeing itself from all the entropy it cannot help producing while alive.

One of the present conceptual trends on the borderlines of physics, engineering, and biology is the systems concept. This term has been used several times in the preceding paragraphs. Physical thinking is barely possible without it. It appears today as an investigative tool in biology and proves pro-

ductive both in concrete applications and in general use of a perhaps more speculative nature (4).

There is no need today to belabor the role of cybernetics as introduced by Wiener in 1948 (5). It has permitted clear formulation and understanding of many fundamental processes in biological systems which were only vaguely discernible before. However, Wiener deliberately neglects thermodynamic concepts which continue to offer significant contributions to the understanding of life processes.

A discussion of information theory may belong more to mathematics than to physics, but it is essential to the understanding of the higher functions of the central nervous system and perception.

Biology is a strange field to the physicist because of the puzzling behavior of living systems in respect to entropy. Epistemologically, however, it is like physics: we want to understand what goes on; questions lead to hypotheses which can be tested by the right kind of experiment. The decision, what is a right and wrong kind of experiment, is conditioned simply and only by its relevance and validity as a test for the hypothesis under investigation.

When we approach medicine, which may be described as biology applied with a specific aim to diseased man, an entirely new factor enters. Medicine deals with disease, which is a malfunction of the biological system. Malfunction relative to what? Apparently relative to normal function. The first difficulty occurs when we attempt to define the normal. This turns out to be impossible unless we turn to an entirely different discipline: sociology. What is health and disease depends to a significant extent on the human environment, the society.

The role of society is not limited to the fundamental function of definition of the norm and hence to the decision when medicine should be required to play a part; it also brings a new meaning to what a right and wrong experiment is. An experiment in medicine, using man as object, may be wrong, although it is eminently right from the point of view which is valid in physics and biology: if for instance it exposes a human being to hazards to health and life. We have now a social ("moral") right and wrong, besides a scientific right and wrong. Medicine is not simply applied physics and biology; it is rooted and intermeshed with sociology.

Lest the medical reader become too envious of the simple life of a physicist and biologist, removed from sociological involvement, let me complicate the matter by the consideration of possible sociological implications of a "right" experiment in physics. Is it right to build a moon rocket, a high energy particle accelerator? The costs are so great that decisions in favor mean draining of funds from other uses, since mankind does not have infinite resources. Even physics, which seems to be methodologically farthest from sociological involvement, is intricately linked with society in the designing of experiments.

Biology and medicine have as their object the understanding and manipulation of living nature in the society of men. Were we to consider as the object of physics the study of inanimate nature, then biology cannot reach its aim

without incorporating whatever insights physics has to offer, just as little as medicine can perform its function without a similar interaction with biology (and hence physics) and sociology. A concise statement of the relationship between physical and life sciences has been given by Lorenz (6):*

This statement not only describes the essential role of physical sciences in the education of a biologist and a physician, but it also implies a program for the contribution of physical sciences to the life sciences in the future. This program may be interpreted as a desire to shell out the physical elements which play a role in biology in order to visualize what is specific and characteristic to life processes as such. This shelling out will contribute to the definition of the field of biology and clarify the paths to scientific investigation in this field. Life sciences have advanced sufficiently to vitiate the mechanistic expectation that such shelling out will leave nothing specific for biology and simply reduce it to physics. A more serious suspicion might be that this program is expected to result in a resuscitation of the "force vitale" concept and to a biological metaphysics. A suspicion of this kind has as little justification as one which would consider the theory of relativity as metaphysics after Newtonian mechanics, since the theory of relativity becomes necessary, for instance, to the understanding of motions at velocities beyond the range considered in Newtonian mechanics. Life processes may require experimental and conceptual tools beyond those provided in physical sciences, but these tools will be inevitably consistent with the scientific method.

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* Our translation:

These considerations determine certain requirements for the knowledge of the investigator. The general biologist has to know physics and chemistry, since the subject matter of his research is by no iota less physics and chemistry than the subject matter of the physicist and chemist. It is true that the subject matter of the biologist contains additionally something else, of a higher order of complexity. This does not relieve him, however, of the obligation to know and to understand the 'lower' inorganic foundations of life processes.

Pathobiology—Definition

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Pathobiology signifies the union of biology (the study of life) and pathology (the study of illness). All organisms float restlessly between a state of health and a state of disease. Although plants, insects, amphibians, fish, and even bacteria and fungi are constantly exposed to injury, most disease entities per se have been associated with and studied in mammals for obvious reasons. Nevertheless, an understanding of the complete biological spectrum in its broadest sense is of great value in the study of disease. The unity of the genetic code, the similarity of structural organelles, and many pathways of intermediary metabolism throughout the plant and animal kingdom demand an appreciation of the value of crossing organismal and disciplinary barriers.

It is well known that many of the most basic principles associated with biology have been elucidated by studying diverse organisms. Examples include: the genetic map studies on drosophila, bacteriophage, neurospora and mutant bacteria; the elucidation of intermediary pathways of protein, lipid, carbohydrate and nucleic acid metabolism, particularly in bacteria; the structure of chromosomes in the salivary gland of drosophila and the newt oocyte, as well as in vicia faba, tradescantia and mammalian tissue culture cells; parthenogenesis in the sea urchin, symbiosis in paramecium, lysogeny, and transformation and transduction in bacteria, all of which may have great significance in regard to response of the cell or organism to its environment.

Specific disease processes are also often most conveniently studied in lower organisms (e.g., tobacco mosaic virus infection in plants, polyoma tumor production in hamsters, leukemia and Rous tumor in chickens, Shope papilloma in rabbits, aging in rotifers, and degenerative diseases in the higher primates).

This concept of pathology as a branch of biology has been presented for the past three years at the annual Pathobiology Conference held each summer at Aspen, Colorado, under the sponsorship of the Committee on Pathology, National Research Council and the National Academy of Science.

Pathology—The Past

The definition of pathology is the study of disease. Traditionally this definition also implied a study of morphological structure on the gross visible level, on the light microscopic level, and more recently on the ultrastructural level with the use of the electron microscope. Although Virchow stressed the cell as the unit of structure in disease, the investigative history of pathology has largely revolved around tissue and organ patterns involving changes in groups

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of cells and alterations in the extracellular spaces. Studies on Inflammation and Repair have included the extravasation of fibrin, fluid and protein into extracellular spaces, the infiltration of white blood cells and laying down of collagen into scar tissue, all these processes markedly altering the normal vascular and extracellular architecture. Two investigators, Metchnikoff and Cohnheim, in the late 1800's initiated an era of physiological pathology which was modified and extended by the American school of pathologists, largely centered in Baltimore, Boston, and Chicago. These included Welch, Councilman, Flexner, Mallory, MacCallum, and Hektoen. Investigations on mechanisms rather than descriptions of disease were spearheaded by leaders such as Whipple, Goodpasture, Opie, Landsteiner, and Rous.

The boundaries of the field of experimental pathology have always been vague and ill-defined. This has recently become most apparent as other pre-clinical disciplines (i.e., biochemistry, pharmacology, microbiology, physiology, and anatomy) have developed almost identical research techniques, theories, and experiments. The importance of pathology, physiology, and anatomy in the early part of this century cannot be denied; indeed these subjects formed the basis of medical practice of this country. The Professor of Pathology was often simultaneously Professor of Histology, Embryology, and Bacteriology. The development of biochemistry by the Hopkins group in England and the attention given this field by organic chemistry students of Fischer in Germany, quickly produced a group of excellent enzyme chemists in the 1930's. Although largely concerned with carbohydrate metabolism, they of necessity studied protein, lipids, and to a lesser extent nucleic acids. Protein and nucleic acid research rapidly progressed in the 1940's and 1950's, along with cytologic ultrastructure studies, and finally, in the 1960's, the emergence of the field of molecular biology encompassed all of these former disciplines. In research, the boundaries and definitions have completely merged. Unfortunately, little progress has been made in extending this concept of molecular, cellular, and organismal biology into the teaching of the biomedical sciences.

Pathology has moved away from the other six basic science subjects and more and more into the clinical area with emphasis on hospital patient services and correlative experimental studies with scientists involved in clinical investigations. At the same time, the preclinical subjects in the medical school have moved closer to the chemistry, mathematics, physics and biology departments of the parent university. This evolution of pathology, as a clinical rather than a preclinical science, was accentuated by the need for highly developed, sophisticated laboratory services in clinical pathology (hematology, clinical chemistry, microbiology) and further stimulated by the division of medicine, pediatrics, surgery and obstetrics into twelve to fifteen separate divisions, all desiring cooperative relationship with students of structure, both in their research and in their responsibilities for patient care.

The explosion of knowledge in biology, chemistry and physics has further widened the gulf separating pathology from the preclinical sciences and pro-

duced tremendous strains in the departmental structure and conflicts in the personnel involved. The situation calls for recognition of the fact that although for organization purposes a single department may remain, the so called "compleat" pathologist in a university setting is no longer a reality. The quality of patient care demanded both in the anatomical and clinical laboratory services, the need for a sophisticated and modern investigative approach in line with other areas in modern biology, and the needs of the community hospital still traditionally staffed by one, two or three pathologists, obligate both administrative and educational leaders to recognize the multiple facets of pathology and provide the personnel, financial, and space supports for these responsibilities.

Pathobiology—Present Scope In Research and Education

For the merging of pathology and biology into the subject of pathobiology, it seems appropriate that the most rapid advances and greatest amount of new knowledge presently available has been gained from the field of cellular and molecular biology, a field which Virchow espoused more than 100 years ago.

The cell remains the unit of function and structure, both in the normal and abnormal condition. Multiple external injurious agents in the cell's environment are constantly exerting an influence on cellular regulatory control mechanisms. These environmental conditions together with the hereditary information contained in the genome determine the cell structure and function at any one time. Lack of ability to maintain controlled homeostasis resulting from various injuries, may either aggravate, diminish, or delete normal metabolic reactions resulting in disorganization of molecular structure. The extent of this disorganization and the capacity of the cell to compensate determine the reversibility of the process. Extensive cellular damage eventually results in extracellular alterations which culminate in gross manifestations called the signs and symptoms of disease.

Disease is concerned with alterations in various metabolic pathways and structural organelles, principally those concerned with nucleic acids, proteins, lipids, and carbohydrates. There are, of course, many other important components of the cell including water, ions, trace metals, and various extracellular hormonal and humoral factors. A basic understanding of the interrelationships, not only of simple enzyme substrate complexes, but macromolecular interactions is necessary before pertinent alterations associated with disease may be documented and their significance evaluated. It has become apparent, however, that injuries are often concerned with synthetic reactions. Latent, dormant nonsynthesizing cells are known to be more resistant to injury than actively metabolizing, dividing cells which have multiple synthetic functions.

Alterations of chemical structure on the molecular level are eventually, in a matter of seconds to days, manifested by changes in organization at the level of the electron microscope. Regardless of the form of injury, a fairly consistent end pattern of disorganization and cell death has been well documented in mammalian cells. In the nucleus this includes breaks, bridges, and clumping of

chromosomes during mitosis and chromatin margination during interphase, blebs and vacuoles, disruption of the nucleolus, and irregularity of nuclear membrane with change in the pore structure. Cytoplasmic alterations include swelling of the endoplasmic reticulum, disruption of the normal ribosomal smooth membrane configuration, breakdown of polysomes, swelling of the mitochondria with disruption of the cristae, enlargement or atrophy of the Golgi apparatus, irregularity of the plasma membrane, formation of autophagic vacuoles, emptying of lysosomes into phagocytic vacuoles, and increase or decrease of pinocytosis, phagocytosis, and other transport mechanisms.

Disease in humans has been classified in the past with regard to etiological agent (e.g., syphilis), to organ (e.g., hepatitis), to an eponym (e.g., Buerger's Disease), or to a descriptive term (e.g., papillary adenocarcinoma). These classifications, although necessary for the present practice of medicine, appear to be out of date in regard to present concepts of injury and repair. It is true that most agents affect multiple intermediary pathways, but the initial pathway affected is often impossible to determine. The same is true in regard to the cellular organelles (i.e., often several organelles appear to be altered almost simultaneously). Biochemical pathways, structural organelles, and physiological functions are so closely interrelated that a hierarchy of processes and organelles most susceptible to injury is impossible to evaluate. It would appear more appropriate to classify cell injury or cellular disease in regard to the etiological agent.

Etiological injurious agents include viruses, bacteria, parasites, radiation, aging, various metabolic inhibitors (analogues, antimetabolites, drugs), and nutritional deficiencies. One or all of these may contribute to an ill-defined disease such as aging. The cells respond to these injuries by one of the four major pathways: 1) production of antibody, 2) division and/or differentiation, 3) extrusion or sequestration including phagocytosis, pinocytosis, lysosomal hydrolysis, 4) alternative metabolic pathways in which the cell adapts to the particular enzymatic block by accentuating a different pathway for which the information is already available.

The response of the cell depends on its state of differentiation, its pattern of metabolism, the amount of information not only present in the genome, but available in the genome. It has different inherent capacities to resist different amounts of injurious agents, and will likewise have different inherent capacities to respond in the manners listed, depending on both its intra- and extracellular environment.

Traditionally, pathology departments have given courses divided into two major sections: General pathology has encompassed both intracellular changes including hydropic degenerations, cloudy swelling, pigment deposition, vacuoles, blebs, metaplasia, hyperplasia, neoplasia and extracellular changes including edema, fibrous and hyaline deposits, and white blood cell infiltrations. Systemic pathology has reviewed a group of diseases based largely on system or organ classification (e.g., pyelonephritis, hepatitis, myocarditis, meningitis).

Many educators have come to believe that the general course in pathology

or pathobiology should be taught on a broad basis utilizing, as discussed in the first section, as many of the phyla of the animal and plant kingdom as are applicable in discussing a principle of biology. Pathobiology should be largely concerned with the major biological changes associated with injury and response. At present, the most knowledge is available concerning alterations in structure and function of the cell, including changes in intermediary metabolism of proteins, lipids, carbohydrates, and nucleic acid, alterations in structure of organelles and most particularly, changes in control mechanisms including induction, repression, feedback inhibition, and allosteric regulations. Undoubtedly as knowledge increases, the same principles can be extended to a society of cells, intact organ systems, and finally to the response of the complete organism itself.

It is firmly believed by many educators from practical experience at the Universities of Colorado, Indiana, and Oxford that a course in general pathology or pathobiology can easily be taught in conjunction with biology in the undergraduate colleges. This will be most feasible in those schools cognizant of the radical changes in biology, chemistry, and the other scientific fields presently being undertaken in undergraduate curricula throughout the country.

Pathology—Its Future

The major challenge confronting pathologists today would appear to be blunt recognition that although pathology departments may continue their present organizational pattern, particularly for means of communication, and most important for the recruitment of individuals into the field, that in any university setting there can be no "compleat" pathologist. A large degree of specialization must ensue. Indeed in quality institutions, this is an acknowledged fact.

We have devoted the major portion of this essay to a discussion of the role of pathobiology in research and education as this would appear to be one of the major areas of deficiency. Individuals with the M.D. degree wishing to pursue full-time university investigative and teaching careers in pathology must have, in addition to one to two years of classical pathology experience, research experience equivalent to a Ph.D. I hasten to add that the myth of the high quality Ph.D. only applies to a few areas in a few university departments throughout the country. The leadership and quality of the prestige departments, recently documented in the Carter Report, "An Assessment of Quality in Graduate Education," has largely obscured the fact that many of the hundreds of Ph.D. programs in the biological sciences are of poor quality and require more drastic development than the M.D. programs which receive the most criticism for backwardness. It would appear of little importance whether a second degree (i.e., a Ph.D. degree per se in pathobiology, biochemistry or molecular biology) were obtained, but the educational equivalent is essential.

In addition, the second year teaching of pathology to medical students

should be restricted to a course in pathobiology closely integrated with the modern biology, hopefully being taught in some microbiology, biochemistry, anatomy, physiology, and pharmacology departments. Whether this integration should be in a block system, on a daily basis, or merely integrated into a general curriculum, is an individual school decision, but general pathology should no longer stand as a distinct and separate course unrelated to the material taught in the other basic sciences.

The teaching of systemic pathology, in the third year, concerned with specific disease entities should be the responsibility of a separate group of pathology department specialists whose research interests and hospital obligations bring them into close contact with the many subdivisions of the clinical departments. Correlative groups of anatomical, surgical, cytological, and clinical pathologists at this level, as already practiced by committee groups in several schools, would produce a standard of clinical correlative teaching of disease not yet attempted in most medical schools.

Such specialization in training is already being carried out to some extent in many medical centers in this country. This is obviously not ideal training for the disappearing group of pathologists who maintain solo practices in community hospitals, and are responsible for the entire range of operations of the laboratory as well as for the educational programs of the entire hospital. Their preparation, traditionally carried in large measure by the universities, almost by necessity requires an entirely different approach which will not be discussed here.

Finally, resident teaching should be separated from medical student teaching and from research training programs. The branches of anatomic pathology associated with the distinct clinical specialities (e.g., pulmonary, cardiac and renal disease) as well as the subspecialities of clinical pathology (e.g., microbiology, chemistry, hematology) have expanded not only quantitatively but qualitatively as well, so that there is no longer a way in which one individual can attain depth in more than one, or possibly two areas in any university. Resident training should be geared to produce real competence in a limited area instead of superficial familiarity with the entire field.

SUMMARY

Medicine has traditionally been extremely jealous of its prerogative of training physicians who are qualified and licensed to practice all facets of medicine, regardless of competence. Medical school educators and investigators have retained this universalist broad prerogative to a point at which it has become detrimental in both teaching and scientific programs. Although it is true that a merging of theoretical, experimental, and applied physics has produced tremendous advances in understanding of this universe, correlative efforts were in the past, and are now in the present, carried out by small specialized groups of individuals.

The greatest advancement of pure knowledge continues to be made by those individuals who spend vast amounts of time and extraordinary energy in a

single field. Interestingly enough, careful examination of prominent leaders advising (although not necessarily administering) the broad policy decisions of government, business, and education in this country, reveals them usually to be men who have attained national recognition of outstanding competence in one field.

Most other professions start from a narrow base and attempt breadth later. Our greatest mistake in pathology has been in starting from a broad base and attempting specialization later, usually too late to be of significance. The field of pathology has become extremely broad, its obligations and responsibilities great, and its training programs confused. Unless a radical change is instituted immediately, with well defined, discrete goals the progress and future of pathology will continue to be marked by uncertainty and disappointment.

The Psychiatrist's Dilemma

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There seems to be ferment in the whole area of medical education. Papers are written, conferences are held, and recommendations for changes in pattern for the education of the undergraduate medical student, the intern, and the resident are many. The continuing dissatisfaction with the end product of our medical schools does not seem to be in terms of the technical aspects of medical education, but with that aspect of medicine which has been designated for so many years as the art of medicine rather than the science of medicine, and there lies the rub.

A recent series of what might be called position papers have been published in conjunction with the founding of The Mount Sinai School of Medicine (1, 2), which discuss limitations in contemporary medical practice and education and project future trends. It is pointed out that there is an increasing separation developing between clinician and investigator: the current image of the physician is impaired by his limited understanding of his role vis-à-vis society and his patient which needs correction by proper education. Increasing specialization and medical education relying more and more upon automated equipment and physical devices will produce well informed specialists with a narrow clinical competence, but this will not replace the continuing need of the patient for consideration of his personal and familial problems. Currently, the public's image of the physician tends to be that he is a technician rather than a healer. Consequently the goals of this medical school will be the imparting of a thorough knowledge of clinical and biological material needed by physicians of the future plus dedication to the personal problems of the patient, his family, and the changing society about him. This, it is hoped, will be accomplished by requiring education in the human sciences throughout the undergraduate as well as the post-graduate years. This will be conducted by scholars in human sciences focused on the medical student, the post-graduate physician, and the house staff.

In Berry's (3) Presidential Address to the Association of American Medical Colleges, he referred to "provocative experiments aimed at making revisions in our teaching programs which are consistent with a growing knowledge of the whole patient rather than just part of the patient." Some variation of this hoped-for process is an element in practically every discussion of medical education that has occurred in recent years. Sociologists, cultural anthropologists, psychologists, economists, philosophers of science represent those areas known as the humanities and are called upon to supply what seem to be the great lack in the graduating physician.

The emphasis is there. The problem is how does one implement it and this

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leads to a series of problems which go to the heart of the process inherent in becoming a physician. Exhortative statements like this recent one of F. Marian Bishop (4) that "the medical educators must somehow impress the medical student with the importance of obtaining information about the 'person' who is his patient" call attention to the problem.

In some medical schools it was apparently recognized that a branch of medicine, namely psychiatry, functions in a manner that is closest to this ideal. Its subject matter is the 'person as a whole' and it operationally takes into account all aspects of the individual, his heredity, constitution, biology, life experiences, personal development, relationships to others and to his community. In addition: "psychiatry has made the study of ideas, fantasies, emotional reactions, behavior, and social adjustments the basis of its empirical interest, and has thereby accumulated fundamental knowledge of the processes by which the human organism adapts, in health and disease, to emotional, physiological, and social stresses. Psychiatry has become a tool by which the basic concepts of medicine (which it is the function of medical education to impart) can be broadened. It is at once an essential part of the science of human biology and a means by which the student's introduction to this science can be facilitated." (5)

The relatively high incidence of psychiatric conditions in various types of populations has been documented in many surveys and studies. Of particular importance to the physician is the frequent occurrence of psychiatric syndromes amongst the patients that constitute his practice. What is being referred to are diagnosable psychiatric conditions that play either a primary or secondary role in individual patients. As an indication of this, one might cite a series of surveys performed at The Mount Sinai Hospital. For instance, a study of 1000 cases (6) from a consultation service at the hospital indicated that in the unselected out-patients who presented puzzling diagnostic features that were examined at The Mount Sinai Consultation Service, 81.4 per cent of the patients were found to have psychological factors as the basis for their complaints and illnesses.

In another study (7), of patients who had been attending non-psychiatric out-patient department services for 10 years or longer, psychiatric disorders were diagnosed in 73.5% of cases. Another study (8) of a group of patients admitted to the medical service indicated that in the survey group some diagnosable psychiatric disorder occurred in 66.8% of cases. A study of the functional (9) relationship of the psychiatrist to the non-psychiatric services indicated that out of 13,811 admissions over a period of 2 years to all services of the hospital, there were 1,319, or approximately 10%, consultation requests for the psychiatrists. The study indicated that the psychiatrist had been asked to become an integral member of the medical team. Sixty-five per cent of the consultations were concerned with the role of emotional factors in the causation, perpetuation or exacerbation of the medical problem and involved the question as to what extent psychotherapy or other psychiatric treatment modalities should be included in the therapeutic program.

This material demonstrates only one aspect of the function of psychiatry in medicine. It might be looked upon as a function relating to the uniqueness of any specialty. There is, however, another aspect to psychiatry and that is its contribution as a basic science, analogous to physiology, by which the physician understands and takes into account the functioning of human personality in relation to health and disease. The latter aspect might be termed, in part, psychophysiology; it represents the most significant factor of an individual's capacity for adaptation to himself, to his environment, and to the people around him. It becomes important, therefore, that the practicing physician have a frame of reference relating to personality structure that is of the same order as the frame of reference relating to physiology or biochemistry. It is not sufficient to be content with some vague notions about the importance of psychological and emotional factors. Our scientific knowledge in this area is as meager in terms of solid data as it is in most other areas of science; however, a number of theoretical systems based on clinical observation and experimentation are extremely valuable.

Conceptually, owing to many factors, modern medicine has become dehumanized. One of the classics in relation to medical education is the famous Flexner Report. Rereading it, in many ways gives one a feeling of *déjà vu*. Some of the problems that were of great importance in the early 1900's are still with us. The report caused a complete reevaluation of our concepts of medical education, doing away with most of the proprietary schools. It raised the teaching and practice of medicine to a new, significant status. It stressed the need for laboratories, although it specifically expressed their relation to clinical medicine in these words: "Nor will laboratory and clinical ends make a genuine whole unless they have throughout a speaking acquaintance with each other." It does seem, in many instances, to be a nodding acquaintance only.

"Instrumentation and laboratory tests too often replace the patient-physician relationship; indeed, there is even talk of diagnosis by computers. In the long run, a much needed integration between basic science and clinical practice has become, instead, a dissociation." (10)

This aspect of the education of the medical student has in one way or another preoccupied medicine for many generations. However, it is only in recent years that this preoccupation has become a specific area of study and research. In the late 1930's the author was part of a team that was involved in the then current methods of teaching from which the following is cited: "The intimate relationship between psychological factors and bodily function has always been recognized in medicine, but the task of conveying the importance of this relationship to medical students has depended more on the individual teacher's interest than on any considered program. To facilitate a study of the problem and to formulate a teaching program, a collaboration between psychiatrists and internists was considered essential." (11)

Teaching and education cannot occur in a vacuum. A certain climate is necessary for the learning process. It is futile to present even the most valid

conceptual frame of reference in terms of 'this is what you ought to do' unless the teacher provides the example of doing it just that way. A department of psychiatry in a medical school isolated from other departments functionally, no matter how many hours it devotes to didactic and clinical teaching of psychiatry, usually fails to impart the necessary knowledge and attitude to the medical student that makes for the complete physician. The essence of the learning process is the eventual automatic functioning of that which is learned.

The role of the psyche as an integrating force within the individual makes it essential that this role be understood within the limits of our knowledge in all aspects of the functioning of the individual. It becomes important then that psychiatry, as psychophysiology, be demonstrated not only by the psychiatrist as a member of a teaching faculty but also by the physiologist, pharmacologist, biochemist, internist, orthopedist, and, in fact, every teacher of basic science and every clinician with whom the student comes in contact.

If it were practical, the department of psychiatry might profitably spend most of its teaching time with the other members of the faculty rather than with the students. It may seem paradoxical, in view of the increased demands for the students' time made by departments of psychiatry in medical schools, to state that the department of psychiatry should have a minimal but sufficient amount of time with the student to teach him some of its theoretical background and to demonstrate clinical syndromes. The student as a future physician will best be qualified if teaching of the basic science of psychiatry comes from the knowledgeable clinician, be he internist or surgeon, who utilizes both precept and example and who could thus become a figure for identification. This would make for the automatic inclusion of the psychological, emotional, and social factors as data to be gathered and reacted to in the diagnosis and treatment of every patient.

Lectures and other forms of didactic teaching are of minimal value. The teaching of what psychiatry has to offer must come through the attending staff on whatever service the student happens to be. Too often what the psychiatrist has taught is undone by the attitude and behavior of other clinicians (12).

In a teaching program, the level of discussion must be such that one neither talks down to the student nor too far above him. A knowledge of formal psychiatry in itself, centering as it does on the overt psychotic and neurotic syndromes, is not sufficient to acquaint the student with the rather intricate psycho-biocultural relationships involved. Theoretically, the average student knows that there is such a relationship, but actually, he has relatively little conviction of its reality. A successful program for the teaching of psychological medicine should begin with the preclinical years.

Simultaneously with the study of function at a physiological level, students should be acquainted with the psychological concomitants. From one point of view, this requires a reorientation of teaching attitudes. Consequently, unless the student comes to his clinical years well grounded in concepts of psychophysical interrelationships, it becomes a difficult task to give him a basic groundwork during the busy and all too short clinical orientation.

One of the major problems encountered in a well rounded course of teaching is the attitude of the house officers and the attending staff. A teacher of psychosocial medicine is in an even unhappier position than the psychiatrist in a general hospital. The house officer is perfectly willing to let the psychiatrist attach a diagnostic label on a patient whom he himself has already recognized as psychotic. As a rule the resident staff, by background and training, is not particularly interested in psychological factors except in very general terms. In the rush of an active clinical service, the house officer and medical student have relatively little time to spend probing into the intricacies of personality organization. A diagnosis arrived at by laboratory techniques seems safe and sure. Psychological investigation is looked upon as dealing with imponderables "not subject to the ordinary criteria of scientific investigation." The student, to a great extent, takes his cue from the house officer who is almost a contemporary in clinical experience. Our experience has been that it is essential, insofar as possible, to have the house officer attend the teaching conferences, and in addition, it is necessary to conduct special seminars dealing with psychosomatic problems for the resident staff and the junior attending physicians. The importance of this step cannot be overemphasized, since it requires sustained teaching effort to familiarize the staff with the concepts involved and to demonstrate, preferably on the ward-patient and in the routine problems that arise, the validity of these concepts.

Perhaps one of the most difficult aspects of the whole problem of teaching in this field is the physician's own attitude toward emotional problems in his patient. Numerous criticisms apparently leveled either at teaching methods or points of view are in reality rationalizations to avoid facing painful subjects. Since such rationalizations involve an emotional rather than an objective point of view, they are most difficult to counter. The fault lies not only with the individual physician and his own emotional problems, but with the type of medical training which he has received. The physician has been trained to look upon death and suffering professionally. Unfortunately this objective attitude frequently is not maintained when the emotional problems of the patient parallel his own.

In Caughey's (13) interesting description of the process of professionalization in medicine, he discusses the concept of "professional infancy" pointing out that the beginning medical student is as unformed as a newborn infant and he emphasizes the importance of the medical school environment and how the student perceives it as well as the impact of key figures with whom he may identify or toward whom he may direct resistance and hostility. He points out that some students attain "professionalization by selection." They approach the study of medicine with enthusiasm, choose a specialty, but maintain continuing interests in other fields, and respect for those engaged in other areas.

Another kind of student follows a pattern of "professionalization by rejection" whereby he loses respect for those in other fields and develops stultifying hostilities which may carry over into his later life as a physician. This complicated process of professionalization is made difficult when the student

encounters open conflict between teachers of basic science and clinical instructors, between community investigators and community practitioners.

Professionalization involves character changes of widespread dimension. Each such situation involves a reverberating circuit response in the medical student and in many instances the confrontation relates to cultural taboos which have to be faced and broken. He further points out that the significance of the needs and conflicts that lead to these taboos have to be re-evaluated and changed into sublimations which permit the physician to feel comfortable in relating to his patients. "These sublimations are perhaps the necessary ingredient for the functioning of the understanding compassionate physician."

We are, therefore, dealing with an interesting and complex series of situations in regard to the role of psychiatry in the education of the medical student. Apparently those aspects of knowledge that should lead the physician to an understanding of the patient as a total person with a psychobiological orientation, involve an educational process that is emotionally charged at practically every level. This involves the student-physician in a series of internal reactions and confrontations, to which he reacts at different times and at different levels with anxiety, frustration, and denial in varying degree. Whereas a great deal of attention has recently been paid to some of the phenomenology of this process, and recommendations have been made from the educator's point of view for various kinds of "learning aids," what seems to be missed is the actual highly affectively toned context within which the educational process needs to take place.

Here then is the dilemma of the psychiatrist, as the faculty member who represents this highly charged context; rejection in its widest sense is very frequently displaced onto the psychiatrist-teacher. Perhaps it is in part the dilemma posed by Socrates who continually urged his contemporaries to "know thyself." We all know what happened to Socrates.

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The Role of Illustration in Medical Education and Medical Progress

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The primary functions of a medical school are the teaching of medicine, the training of physicians and, to some extent, the advancement of medical knowledge. As medical knowledge has expanded with geometrical progression, the methods of disseminating this knowledge have by no means kept pace. The medical literature of today is more graphic than that of some thirty or forty years ago and various audiovisual teaching aids are being employed with increasing frequency, electronic teaching devices are slowly being introduced but the employment of such methods and devices still lags. The old adage that "a picture is worth a thousand words" is frequently quoted and too seldom applied.

Comprehension consists, to a considerable extent, in being able to visualize or create a mental image of a subject. Thus, if we say we understand the anatomy of the knee joint, we mean that we can visualize the ends of the femur and tibia, the semilunar cartilages, the cruciate ligaments, the quadriceps tendon, and so forth. If we say we understand the pathology of acute cholecystitis, we mean we can visualize an inflamed gallbladder in its gross and microscopic aspects. Blind memorization without visualization can scarcely be called true comprehension. What then are the functions of medical illustrations? It seems to me that they are threefold.

First, pictures help an individual who is studying a subject to gain a comprehension of it. As he makes a sketch or drawing or diagram, or studies one made by someone else, he gains a mental image of it. I am reminded of an incident that occurred some time ago when I was planning to make drawings of a certain subject. As is my practice, I first studied the literature on the subject rather thoroughly but the more I read the more confusing the subject became because there seemed to be such diversity of terminology and of concept. I did, however, come across the writing of a man in England who seemed to have a thorough grasp of the topic. I felt that I would not be happy making these drawings without first talking with this man. I wrote to him and was invited to meet with him. We spent several pleasant days together discussing the subject and then I returned home and made the drawings. Several months later this professor visited the United States and telephoned me. I told him I was delighted that he was here because I had finished the drawings and would like to have him review them. He came to my studio and, after pleasant amenities, I spread the drawings before him. He studied them in absolute silence for some ten to fifteen minutes and I thought to myself, "I must have made some very serious errors and he is too embarrassed to tell me about them." When he finally spoke, however, he said, "It is quite amazing to me. I know every fact that you have depicted in these illus-

trations, indeed I told them to you, but when I see them organized graphically in this way, I gain a different concept of the subject."

Thus, illustrations are an aid to comprehension, not only for the novice or student but also for the expert. They are an aid to clear and logical thinking. They are stern disciplinarians in the sense that one may write around a subject but one can scarcely leave holes or blank spaces in a picture.

Second, pictures serve to transmit ideas from one mind to another. We transfer the images we have via the paper to the mind of another individual. They are thus an aid to the efficiency of teaching, a sort of "teaching catalyst." This was pointedly demonstrated by my experience in the army during the last world war. When I was first inducted no one could understand how pictures could be applied in the training program. Then one day a General called for me. He handed me the Army First Aid Manual of some 300 or more pages of text material and said: "This is impossible. We are allotted eight hours in which to teach combat troops how to take care of themselves or their companions if wounded. It would take six months of a full-time course to teach them the contents of this book. Let's see what you can do to simplify it." I planned a manual of exemplary illustrations with accompanying concise texts. It was an immediate success. The trainees could learn quickly from these pictures and, more important, they could remember in the stress of combat what they had seen in the pictures. At that point, the Medical Department of the Army discovered the value of illustrations. From that time requests for illustrated manuals poured in. Among these was a request for an illustrated manual for the training of x-ray technicians. In civilian life it had taken two to three years to train an x-ray technician but the army wanted to train them within several months. The pictorial manual which we prepared made this possible.

When there is so much knowledge to impart to the burdened medical student and when the teaching curriculum is so crowded, it seems logical to employ the devices which the army found to be efficient.

Third, pictures serve to transmit ideas from one generation to another; that is, to preserve ideas for posterity. If we look at the work of the progressive medical and anatomical thinkers of the past, many had recourse to illustrations to express their ideas. Witness, for example, the classical works of Eustachi, Varriolio, Bartholinus, Santorini, Scarpa, Velpeau, Vesalius, and Leonardo da Vinci.

The latter two described functions of medical illustrations, namely, the transmission of ideas from one mind to another and from one generation to another, have indeed played a role in medical progress. In the past few decades many far reaching and epochial discoveries have almost revolutionized medical and surgical practice. Nevertheless, true medical progress has been a step by step process wherein men added blocks of knowledge upon foundations which may have been laid by men of another generation or even another era in a different part of the world speaking a different language. Medical progress has thus been a cooperative enterprise. This cooperation has been

made possible by the communication of ideas from one mind to another, from one generation to another, from one era to another. The media of communication have been twofold; the written or spoken word, and pictures of one type or another. Both are essential. Pictures pinpoint and make graphic the meaning of the written word while the written material explains and expands upon the illustration. Even in earlier days when the reproduction of pictures was painstaking and tedious, progressive physicians and scientists employed illustrations to express their ideas. In this modern day when pictorial reproduction has been so perfected, it is all the more practical to utilize medical illustrations in teaching.

In view of the vital role of medical illustrations in medical progress and for efficiency in medical teaching, it is deplorable that so little recognition has been given to the subject in the organization of the modern medical school or teaching hospital. A few progressive institutions do have a well organized department of medical illustration but many outstanding schools and hospitals have none or at most a very poor one. In some of these institutions one finds the department of medical illustration in a corner cubbyhole wherein a lone underpaid artist struggles to fulfill both the art and photographic needs of the entire staff. I am certain that the directors of such medical institutions feel that they are progressive in having established a department of medical illustration. To me this is unfortunate because it demonstrates the total absence of the concept of the role of illustrations in modern medical education. Millions of dollars and thousands of man-hours may be spent in such institutions in the advancement of medical knowledge and practice but such development of new ideas and new methods is of little value unless this information is disseminated both to the physicians who can apply it and to other investigators who may advance it. Yet so little regard is given to the methods by which this information may be disseminated. As a result, a physician or scientist today who may have something to say to other members of the profession or to students and who writes an article or a book, must not only spend many hours in composition with little or no recompense but must often pay for illustrations or else make do with inadequate "do it yourself" diagrams. Even when he is willing to pay for the illustrations he is hard put to find a qualified artist.

The failure to recognize the importance of good illustration is indicated by the fact that there are today in this country only about eight schools for training in this field and that these schools take only from four to eight students each year. It is difficult to find placement for even this small number because so few institutions have allocated sufficient funds for this purpose. Yet the interest in the field is great. Every year I have numerous young people interested in entering this field talk to me about it but I must discourage them because of the limited opportunities. In contrast, large industrial firms, such as electronic and aerospace companies, have well organized art and photographic departments in order to graphically record their work.

An article of this type should be constructive as well as critical. I propose

therefore that every medical school and teaching institution recognizes the broad subject of communication.

Many devices and media, both new and old, expedite communication. These include drawings and paintings, charts and diagrams, photographs in color as well as black and white, models and mouldages, film strips, motion pictures, and closed circuit television. But pictures of one type or another are the most important because they are most practical, most economical, most ready at hand, and most available for restudy. They are as important a tool for the educator as is a saw (we might better say an electric saw) to the carpenter. Every modern medical teaching institution should have a well implemented and staffed department of medical communication or "Department of Medical Illustration" as an essential in its program. It must be included in the budget just as the Department of Medicine or of Pathology.

The directors of many institutions feel they cannot afford such a department. Such thinking is the result of regarding medical illustrations as a luxury rather than a necessity. Illustration must of necessity be tailored to the needs of each institution. Several excellent departments now functioning may serve as models, specifically at the Mayo Clinic, at the University of Illinois, and at the Johns Hopkins School of Medicine. I am sure there are others. Such a department should have facilities not only for making illustrations but also for filing and recording them.

There is still another phase to the application of art to medicine. Earlier I pointed out that illustrations are an aid to thinking and comprehension. Accordingly, the medical student and physician should be encouraged to make drawings and diagrams for his own edification. Unfortunately, in our elementary and high schools as well as colleges many students are told "You have no talent" and they then continue through life with the belief that they cannot make drawings. This is a psychological handicap, for almost anyone can express his thoughts in some type of diagram or drawing and will find it of great benefit to do so. It would be most desirable for medical schools to offer an elective or required course in drawing. Not every student will learn to make elaborate renderings or paintings, but he will make drawings and acquire the habit of doing so. One of the unfortunate developments in our progressive educational system has been the overuse of the "true or false" type of examination. Thus the student does not express himself either in words or drawings. It might be advantageous if the students in examinations would be asked on occasion to make a drawing or diagram in response to a question.

A program such as here outlined would aid the student in remembering subjects, the instructor in teaching, and the research worker or physician in communicating his ideas to others in his field.

SUMMARY

Medical illustrations expedite the learning process, facilitate teaching and play a vital role in the progress of medicine. An *adequate* department of medi-

cal illustration is a necessity, not a luxury, in every modern medical school and teaching hospital for the dissemination of medical information is of equal importance with its accumulation. Every medical student and physician can learn to make drawings of some type as an aid to comprehension, clear thinking, and expression.

EPILOGUE

The Goal

Hans Popper, M.D.,* and David Koffler, M.D.†

The major goal of new and old medical schools is to produce physicians whose training is consonant with the future needs of society. Medical educators have, therefore, to anticipate areas of significant social change and predict the effects of these changes on the structure and practice of medicine. This responsibility weighs particularly on new medical schools because of the greater opportunity for experimentation. This responsibility is even heavier if the new school is in a large metropolitan center in the United States because here the society of the future seems to be better exemplified than anywhere else. By 1980 the population will be concentrated predominantly in cities, resulting in a further vast increase in technological resources in these centers. Thus, such a new school can rely even less on previous experience, but should serve as laboratory where the advances in medical care are to be tested.

The medical school may address itself primarily to the immediate relief of the medical manpower shortage or to medical needs 20 years hence when the first graduates of the school will approach the peak of their professional career. The immediate need of the community is for the general practitioner, family physician, or primary physician (1) who is rapidly disappearing from the medical scene. It is probable, whether desirable or not, that this general practitioner will have largely vanished in the next 20 years, at least from the large urban centers. Medical educators have the responsibility for producing physicians and allied health personnel trained in order to meet the expanding and justified medical needs of the population. In academic institutions, moreover, they must develop such systems of medical care by trial and error experimentation.

The Prediction

The group responsible for the design of the philosophy of the Mount Sinai School of Medicine has, therefore, considered prediction of the future as the most important factor in shaping the curriculum, and in outlining research problems in the area of community medicine. The key points, stated several years ago (2), are even more applicable today:

1. The exponential increase in the amount of medical information makes it impossible for an individual to retain all essential facts.
2. The increased use of quantitation in biology and medicine changes methods of medical practice.

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3. The development of a unity of biology blurs the borders among biological disciplines and permits the application of similar principles to various branches of biology.

4. A clinical science is emerging and applies at the bedside the exact techniques and heuristic principles used in basic science.

5. Technologic sophistication in medicine is rapidly developing.

6. Specialization narrows the field and enhances the application of knowledge from pertinent basic science; moreover, observations derived from research in the limited field assist in service activities and vice versa.

7. The importance of behavioral and environmental factors is recognized in the prevention, diagnosis, and management of disease.

8. More potent pharmacologic and manipulative techniques are utilized and entail dangerous side reactions, which may create serious ethical problems during the initial testing stages.

9. The age distribution shifts to an older population, which may be partially incapacitated.

10. Tools for recognizing disease in a preventable pre-symptomatic stage are being introduced. (This is another reason for the transformation of the hospital from a temporary shelter for acute disease into a health center for continuous care.)

Three additional trends representing facets of the same problems deserve emphasis at this time:

First, when the interest of society in medicine and health care rises together with the expectation of the best possible medical care, the administration of health care becomes more sophisticated, and the overall responsibility tends to shift from the physician to the social scientist. The latter, rather than the practitioner of medicine, may thus dominate the apex of the health care pyramid. Several forces favor this development which deserve recording, although not necessarily approval. The social and governmental sciences are acquiring more and more scientific veneer and nomenclature, but they are still far from precise documentation of theory by experiments. The approach which characterizes the basic scientist and hopefully the clinical scientist does not yet exist for the social scientist. Nevertheless, he is acquiring equal status with the basic and clinical scientist in the design of health care. This is enhanced by the reluctance of a large segment of the medical profession to compete with the social scientist in governmental decisions concerning medical problems. The governmental approach de-emphasizes basic science and stresses the more immediate application of medical discoveries. Moreover, the policy-making administrator, being a social scientist rather than a physician, whatever his academic degree, will be more concerned with the interests of society as a whole than with those of the individual patient. The importance of a disease as reflected in the time it occupies in a curriculum and the amount of funds devoted to its study becomes related to its incidence and impact on society. In contrast, the individual is the primary concern of the physician, while, for the clinical scientist, the understanding of rare "exotic" disease is a challenging experiment of nature

which permits a basic understanding of disease processes. The conflicts, however, among social scientist, physician, and clinical scientist are beneficial from the point of view of reaching a consensus useful in teaching and patient care.

Second, the emergence of the concept of the regional center or complex dedicated to a single disease group may alter not only the relations between patient and physician, but also among physicians themselves, and, therefore, significantly change the structure of medical education and practice. The concept implies concentration of equipment and specialized knowledge for the management of major diseases, such as heart disease, cancer or stroke, in one major medical installation, usually university controlled. This center is to serve a large geographical area with affiliated hospitals referring patients to the center. The economic implications of this system are of limited interest here. More important for the physician in training is the fact that the physician in charge of the center will control the most important tools for the management of disease. This might eliminate the present conflict between the pre-eminent clinician who, as private practitioner, is the acknowledged leader in conduct of medical care and the full-time chairman of a department or unit. The latter is usually a clinical scientist with his primary interest in investigation and is frequently only tangentially concerned with patient care. At present, the young physician is torn between these two idols which he wishes to emulate. In the regional center, however, these divisions will probably merge. The institutional chief being custodian of complex equipment and specialized medical knowledge will not permit himself the luxury of a primary research career, but will be encouraged to consider the administration of medical care as his major function. The private practitioner may thus play a lesser role, because the best facilities in patient care exist in the center. Hopefully the idol for the budding physician will be a new breed of medical leaders, a specialist who combines clinical excellence in a circumscribed field, an understanding of basic quantitative problems of this field, and conducts research in it. Postgraduate and predoctoral training programs may also utilize the center as sources of education in both basic science and clinical medicine.

While the leading medical schools in the country do, at present, emphasize as a measure of their excellence the number of professors in full-time medicine which they have developed, they may in the future also refer to the men in top positions in the centers as their most important products.

Third, the development of computer techniques may alter the practice of medicine on different levels. They serve primarily as a labor-saving device when used for data retrieval, although these techniques may also allow the synthesis of new information. The simplification of record keeping and the ease of reproduction will make available to the physician information which sometimes is obtained only with considerable difficulty and with great time loss. The culmination of this principle is the national storage of the medical history of every citizen, including such readily stored facts as immunization records, hospitalization records, laboratory findings, operative results, etc. The

existence of such a national depot readily accessible to every practicing physician is technically possible today. Problems of ethics enter, however, since certain information of damaging nature such as criminal records or temporary mental disease could not be eliminated from the data.

Another area of computer application in medicine is the conduct of experiments by analogue computer which might allow a radical reduction of the number of experiments, frequently from an excessive to a manageable level. This is more a problem of research than teaching.

The utilization of cybernetic techniques in the diagnosis of disease is most critical for teaching. The development of computer techniques may be ready for this approach, although this area of medicine is not easily programmed. Computer analysis of laboratory data such as biochemical and even electrocardiographic findings should entail no difficulty and such applications are rapidly being developed. Two major obstacles, however, arise in the utilization of clinical and even pathological observations in diagnosis. One difficulty is that these observations cannot, at this time, be quantitated or even clearly be defined by words. Moreover, diagnoses, based on clinical observation, are derived only in part from conscious application of definite criteria which may or may not be quantitated. Frequently, however, the diagnoses are based on intuitive subconscious association of observations. The physician can hardly define or teach these associations. They are translated with difficulty into exact information and they surely cannot be stored in the computer. This brings us to the theory of learning and a psychological investigation of the physician in the process of diagnosis or decision-making. Herein lies the separation of medical art, based on intuition, from medical science. Decades of study will be required to verbalize and quantitate many of our observations and to raise diagnostic association from subconscious to conscious levels. Success in these endeavors will modify the conduct of medical teaching more than any preceding development resulting from progress in biology.

The Challenge

The shortage of medical manpower on all levels—specialists, generalists, nurses, technologists and biomedical engineers—deserves no further comment and has priority in government and social thinking, even at a time when the nation's resources are stretched to the limit by defense needs. The solution lies in the organization of a system of health care which preserves dignity and provides enthusiasm for health workers, and attracts young men and women to the field, with avoidance of frustration resulting from work which is either uninteresting or for which the worker is not prepared.

The physician of the future, as the primary product of the medical school, will have to develop attributes which were previously not taught in medical school, although many schools are now experimenting with curricula meeting these needs.

The Mount Sinai concept (3) embodies these considerations by the definition of a new tripod requiring balance. It supplements the old accepted tripod of

patient care, teaching, and research by defining the teaching leg by the following three aspects:

1. Emphasis on quantitative biology in medicine, so that the physician becomes a superb technician "equally equipped for treatment and for prevention of disease," but with an unavoidable tendency for specialization.

2. Concern for the patient as a whole with his mental and physical problems as well as those of his family, acquired by "continuous education and better exposure to teaching in sociology, psychology, social anthropology, economics, ethics, and philosophy of science." The knowledge acquired from psychology and sociology may shelter the student from the extremes of cynical disregard of or over-identification with the physical and mental pains of the patient.

3. Interest in society as a whole and in a patient care system in which all justified medical needs of every member of the society are considered. This is now frequently summarized under the term "community medicine" dealing with prevention of disease and logistics of patient distribution.

In all three aspects of this tripod, the medical student will have to be trained to work together with allied health professionals. He will depend on the basic scientist, ancillary technicians, and the biomedical engineer for problems in quantitative biology, and in the area of patient concern on the behavioral scientist and the sociologist. The latter is even more important in "community medicine" where the student will be particularly concerned with the allied health professionals conducting some of the medical care now assigned to physicians.

The necessity for training the M.D. candidate to work together with the members of the health professional team is a major reason for educating all members in the same school, which broadens the medical school to a school of higher learning in the health sciences. Its curriculum will depend on the composition of the health team of the future. The role of the technical or medical basic scientists such as biochemist, biophysicist and their technicians, of the behavioral scientists, and even of the economists and sociologists concerned with health science problems is clear. Less well established or even accepted is the role of clinical assistants concerned with supervised patient care for partial replacement of the physicians' services.

The nursing profession has accepted the responsibility for much of the institutional care which in previous years was, and in Europe still is, the sole function of the physician. In some countries, particularly in the eastern part of the world, poorly trained physicians are being produced, whose limited training prevents them from becoming specialists and makes them satisfied with primary medical care. In fact, this "feldscher" is an independent practitioner whose responsibility to refer a case to better trained physicians or medical installations rests with him alone. In this country, such limited training is objected to on practical and philosophical grounds. Moreover, advancements in techniques should make it possible to develop a health team in which clinical technologists or assistants with college or even graduate degrees might serve as the initial contact with the patient in institutional and home care. They may

use screening tests in the patient's home and thus avoid excessive hospitalization and visits to the outpatient department. The system of a free enterprise society, also, demands upward mobility for the members of the team on the basis of additional training and on demonstrated efficiency in practice. The education of these clinical "technologists" in an institution of which the medical school is one part entails at least three advantages:

[1] It permits the training of medical students in cooperation with the clinical "technologist" as he would be expected to perform in his future practice.

[2] It makes the upward mobility, just referred to, possible, so that the clinical technologist might advance to become an M.D.

[3] (and probably most important) The development of such teams, by trial and error, is becoming one of the most important functions of a medical school, as part of a health science oriented school of higher learning or university. To leave the experimentation with these systems in the hands of social scientists results in an unfavorable reception by the medical profession and an undesirable reaction by the patient. If medicine is to respond to its challenge, it not only will have to develop quantitative biology and a cybernetic approach to diagnosis, but, of equal importance, it will have to demonstrate the usefulness of health care teams in the confines of the university hospital.

The medical schools will have to find a replacement for the revered general practitioner. At present, it might appear challenging to construct a system consisting of four categories:

1. The clinical technologist who would have the first contact with the potential patient, comparable to the role of the corps man in the armed services.

2. The specialist steeped in basic and clinical sciences, to handle more complex medical problems.

3. The psychiatric social worker to take care of the large number of emotional problems deserving attention.

4. The medical specialist in patient distribution and logistics who conducts his research, service and teaching, probably in this order, to oversee the system.

Computer techniques after they have been worked out will assist in clinical management, particularly in categories one and four.

The Solution

The challenge will be met differently by different institutions, depending on local circumstances and preferences. Agreement will probably evolve as to the construction of a health science school of higher learning, comparable in some respects to the technological science integration at the Massachusetts Institute of Technology and the California Institute of Technology.

These health science schools may be part of "multiversities" concerned with all aspects of higher education or may be independent institutions capable of broadening into universities similar to the institutes mentioned above. The graduate school of Biological Sciences can easily be integrated with the medi-

cal school, as this will facilitate the interchange of students between the two schools without loss of credit or prestige. For example, the medical student may continue in biochemistry or in another life science. The coordination of graduate schools devoted to sociology, psychology or other aspects of social sciences and humanities relevant to health may be a greater problem. The greatest existing difficulty is the integration of schools of clinical and laboratory technologists although hopefully these barriers will fall since dental and public health schools are now being integrated with medical schools without difficulty.

The problems of curriculum in the medical school will be primarily determined by the interest of the staff and the type of students, and no brief can be made here that our own solution (4) is better than any other, although universal agreement probably exists with three principles: namely,

1. The unity of biology, including basic medical sciences and clinical sciences.

2. The need for some element of integration:

- a. of the teaching space, as exemplified by the multidisciplinary laboratories;

- b. of the teachers by unifying various departments and courses;

- c. of basic science with clinical medicine and both with social sciences and humanities;

3. The attempt to imbue the medical student with the spirit of a graduate student rather than of a trade school student by giving him adequate time (elective periods) to study chosen fields in depth. We cannot forget however that any licensed physician becomes a threat to society if he does not command a core of information comparable to that given in a trade school. The identification of this core so far is not completed.

Whatever the specific system is, however, the product will probably reflect the enthusiasm of the teacher and the initial quality of the student body rather than any specific teaching technique.

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Three-Dimensional Cone-Generated Computer-Drawn Vectorcardiograms

Louis Brinberg, M.D.

An article in press (1) describes a technique by which three-dimensional vectoreardiograms are drawn by a computer-recorder. It also proposes that a loop in space be displayed by a sequence of conic figures. The program for this display has been completed, and an example is shown in figure 1, in which a normal QRS loop is referred to a spherical frame of reference.

On the sphere, the graticulations are at 30° intervals. The X axis is included to orient the reader. Its positive pole is marked by a solid circle, and its negative pole, by an open circle. Longitude is measured from the left and ranges from 0° to 180° . The anterior hemisphere is positive; and the posterior, negative. Latitude ranges from 0° to 90° . The inferior hemisphere is positive; the superior, negative. The observer axis is -20° ; -20° . The program calls for the shaft of the maximum vector to be drawn in, and it is shown at -9° ; 21° (longitude; latitude), which is the electric axis of the loop.

The loop is generated by a point, which lies at the center of a small circle. The plane of the circle is at all times normal to the path of the loop and forms the advancing base of a right conic figure. The trailing apex follows the line of the loop, and the surfaces of the conic figure are contrasted. The outer is black, and the inner, white. The figures are spaced at 2.0 millisecond intervals, and the three-dimensional display, which is drawn to perspective, is effected by their attitudes and positions with respect to each other and to the origin at the center of the sphere.

The display of figure 1 was drawn at electronic speeds by the Stromberg-Carlson 4020 computer-recorder from taped orthogonal leads of a normal subject that had been passed through an analog-digital converter and a programmed IBM 7094 digital computer. The entire procedure is tape-to-tape, and the same program is used for all subjects.

It is possible to eliminate tapes and intermediate "off line" steps. Patient data can be passed directly to a general or special-purpose computer-recorder by way of an analog-digital interface and processed "on line." Instrumentation for such an arrangement exists, and a piece of equipment can be assembled that will display three-dimensional vectoreardiograms in "real time" at the bedside.

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From the Division of Cardiology, Department of Medicine, Mount Sinai Hospital, New York, N. Y. Supported by Grant 5 ROI HE09987-02 from the National Heart Institute of the United States Public Health Service. Programming by Digital Programming Services, Incorporated of Boston, Mass.

RADIUS	OB LONG	OB LAT	OB DIST	MVMAG	MV LONG	MV LAT
440.0	-20.0	-20.0	6600.	1111.8	-9.1	20.9

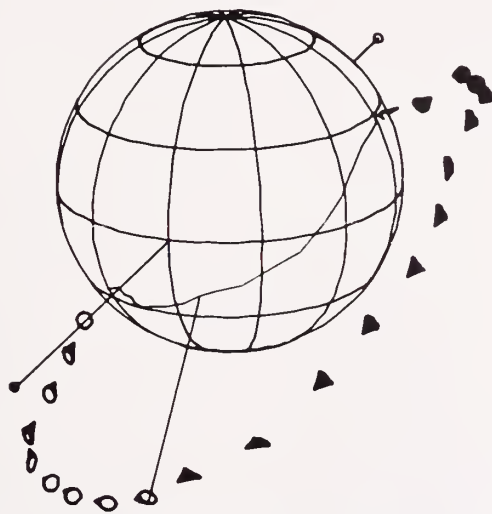


Fig. 1. Cone-generated vectorcardiogram of a normal subject. The cone has an advancing base and a trailing apex and is a three-dimensional analogue of the two-dimensional tear-drop of planar vectorcardiography. The X axis is included to orient the observer. Its positive pole is marked by a solid circle, and its negative pole, by an open circle. The shaft of the maximum vector is shown, and the track of the instantaneous vectors is traced on the surface of the sphere. A portion of the titling that accompanies each display is placed above the figure. It states that the radius of the sphere is 440 microvolts, that the observer axis is $-20^\circ; -20^\circ$ (longitude; latitude), and that the observer distance is 6600 microvolts from the center. It also supplies the computed spherical coordinates of the maximum vector, which are (1111 microvolts) ($-9.1^\circ; 20.9^\circ$) (magnitude) (longitude; latitude).

Unusual Problems in Surgery

LEWIS BURROWS, M.D. AND JULIUS J. LEICHTLING, M.D.

CASE NO. 5

Neonatal Bowel Necrosis And Peritonitis

Neonatal peritonitis is rarely due to ischemic necrosis of the bowel. The mortality is alarmingly high. In the series of 172 cases reported during the past year from Childrens Hospital in Columbus, Ohio, 78% died. Ischemic intestinal necrosis was the cause of peritonitis in 21 patients; most of these cases were associated with malrotation and volvulus or internal hernia. There were no survivors in this group (1).

In 1967 Birtch, Coran and Gross reported a series of 99 cases of neonatal peritonitis (2). Only 4 had areas of local bowel infarction; 2 were thought to be secondary to trauma; 2 had perforations of diverticula.

We are presenting a case of neonatal peritonitis with localized bowel necrosis which was apparently caused by a peritoneal band compression of the mesenteric vessels. The preferred method of bowel resection with end-to-end anastomosis was unsuitable in this case, and a surgical procedure initiated 75 years ago proved to be lifesaving.

CASE REPORT. A female infant weighing 3220 gm, and measuring 50 cm from crown to heel, was delivered after a six hour labor

by assisted breech extraction on February 16, 1967. The mother was a para 1001. The apgar score was nine.

Physical examination at birth was entirely unremarkable except for ecchymotic areas of the buttock and perineum. The abdomen was soft and not distended.

The infant retained clear fluid feedings and passed normal meconium during the first 24 hours. On the second day the baby was noted to be slightly icteric and lethargic. She began to vomit small amounts of greenish yellow material after each feeding. At this time, the rectal temperature was 98.8 F, the pulse was 140 beats per minute, and the respiratory rate was 56 per minute. The abdomen was moderately distended and the veins of the abdominal wall appeared engorged. No abdominal masses were palpable and no bowel sounds were heard. A rectal examination was normal.

The hemoglobin level was 18.4 gm/100 cc; hematocrit level 49%; white blood count 4,400 with a differential count of 30 segs., 17 stabs, 44 lymphocytes and 9 monocytes. Serum bilirubin was 5.5 gm total, 0.4 gm direct. No Rh or ABO incompatibility was noted.

Supine and upright x-rays of the abdomen revealed moderate gaseous distention of small and large bowel loops. Fluid levels were not delineated with certainty.

The working diagnosis at this time was paralytic ileus of unknown origin, possibly sepsis originating from the umbilicus. The baby was treated with intravenous fluids, nasogastric suction, penicillin and kanamycin.

Twelve hours later the abdomen was noted to be more distended. The pulse rate was 160 beats per minute and the respiratory rate rose to 70 per minute. X-ray studies were repeated and demonstrated increased dilation of the bowel loops with definite fluid levels (Fig 1). A barium enema demonstrated a normal colon which filled completely. Evacuation of the barium was poor.

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Case No. 5, Fig. 1. Plain upright radiograph of abdomen showing many dilated loops of intestine with fluid levels.

At this time a small area of cellulitis about the umbilicus was noted for the first time. Needle aspiration of the peritoneal cavity was performed and 10 cc of tan turbid fluid was obtained. A stained smear of the aspirate demonstrated numerous polymorphonuclear leukocytes but no bacteria were seen.

OPERATIVE FINDINGS. Under general anesthesia the peritoneal cavity was entered via a right paramedian incision. About 40 cc of thin tan pus was aspirated; subsequent culture grew *E. coli*.

The entire bowel from the ligament of Treitz to the midtransverse colon was uniformly dilated and cyanotic. Twenty-two centimeters of the mid ileum was dark red exhibiting multiple hemorrhagic areas mixed

with areas of yellow or greenish color (Fig 2). The cecum was normally fixed in the right lower quadrant. The small bowel mesentery was normal in position and rotation. Careful examination of the vessels at the root of the mesentery revealed no evidence of thrombosis, although any pulsations felt were extremely feeble and there was evidence of venous congestion. This was in sharp contrast to the normal pink color of the left colon where excellent pulsations could be seen in the mesenteric vessels.

Situated at the root of the mesentery at the ligament of Treitz there was a thickened peritoneal band which stretched across behind the superior mesenteric vessels and appeared to compress these vessels. The peritoneal band was divided and 45 cm of



Case No. 5, Fig. 2. Photograph taken at the operating table showing loops of dilated bowel with hemorrhagic and necrotic changes.



Case No. 5, Fig. 3. Photograph of the baby taken after the operation showing umbilical clips occluding both stomas of the double barrel enterostomy.

ileum were resected. The small intestine remaining after resection measured 59 cm. The color of the remaining small intestine and right colon improved gradually and after about 30 minutes it changed from blue to a dark red.

A double barrel Mikulicz enterostomy was fashioned by sewing the remaining loops of ileum together along the antimesenteric border for a distance of 6 cm. This was brought out through a stab wound in the right lower quadrant and fixed by suturing the peritoneal and fascial layers of the wound to the bowel. Each stoma of bowel was occluded by a metal umbilical clip (Fig 3).

A Stamm gastrostomy was performed. The peritoneal cavity was irrigated with saline and the wound was closed in layers. Sixty cubic centimeters of blood was transfused during the operation.

HOSPITAL COURSE. Intravenous fluids, albumin, penicillin and kanamycin were administered in the immediate postoperative period. After 36 hours, the umbilical clips

were removed and a spur crushing clamp was applied to the common wall between the two loops of ileum. The abdomen deflated over a period of several days and feeding by gastrostomy was begun. The spur sloughed leaving a free passage between the proximal and distal bowel.

On the 11th postoperative day a double layer closure of the Mikulicz enterostomy was performed intraperitoneally. Postoperatively, 9 to 10 loose stools per day were passed per rectum but after two weeks the stools became normal and numbered 4 to 5 per day starting 10 days after the closure of the enterostomy. The weight gain was progressive. A barium meal showed a free flow of barium through the small intestine and colon. The transit time was not unusually rapid.

Pathological examination of the resected specimen showed evidence of acute peritonitis with large areas of ulceration and congestion as well as areas of frank necrosis (Fig 4). A remarkable and unusual finding was the presence of marked submucosal



Case No. 5, Fig. 4. Operative specimen of resected bowel. Note obvious necrosis of central loops.

thickening and fibrosis throughout the entire length of the specimen.

DISCUSSION. In neither of the two large series of cases of neonatal peritonitis previously cited was compression of the mesenteric vessels by causes other than volvulus or internal hernia mentioned. Ratner and Swenson reviewed the literature of mesenteric vascular occlusion in infancy and childhood; they collected 19 cases including 5 cases of their own (3). Only one survivor in the neonatal period is recorded. This patient had an infarction of the middle portion of the small intestine. There

was no malrotation, volvulus or obstructing intestinal band. In three cases mesenteric bands which compressed the vessels are mentioned.

Of interest in our case was the short length of the small intestine. The total length of small bowel from the ligament of Treitz to the ileocecal junction was just over 100 cm. The average length of small intestine in a normal newborn measuring 50 cm is 284 cm with a range of 140 to 440 cm. Shortened intestinal segments have been associated most frequently with omphalocele, atresias and malrotation.

Pathological examination of the specimen in our case revealed two processes to be evident. First, there was the marked thickening and fibrosis of the submucosa. This fits well with the probability of prolonged intrauterine ischemia of the bowel as a cause for the thickening of the wall and the shortening of the entire small bowel. The second process was the acute necrosis of the segment of ileum. It appears probable that the peritoneal band which caused the partial obstruction of vascular supply to the bowel in utero became totally occlusive after birth. The distention of the intestines due to air swallowing and feeding might have played a role in further compression of the vessels to the point of occlusion. The improvement of the circulation following the division of the peritoneal band lends support to this hypothesis. One can only speculate as to why only a localized portion of intestine became irretrievably compromised. It is quite possible that the collateral circulation from the coeliac axis above, and the inferior mesenteric artery below, left this area in the middle of the intestine with the weakest collateral support.

CLINICAL MANAGEMENT. The diagnosis of ischemic bowel necrosis is often difficult. However, once peritonitis sets in, regardless of the etiology, the findings are fairly constant. Abdominal distention is present in practically all patients (1, 2). Vomiting and failure to pass stool are present in 75% of cases. Shock and respiratory distress are common findings. The x-ray picture depends on the underlying cause. Perforations may ex-

hibit pneumoperitoneum, the calcific flecks of meconium peritonitis, or evidence of intestinal obstruction secondary to atresias. In our case the findings were rather non-specific and the diagnosis actually became evident after needle aspiration of the peritoneal cavity.

A right paramedian incision was used because the exact location of the pathology was not known. The situation which presented was that of small intestine of marginal viability and frank peritonitis. Although primary anastomosis has been successfully performed in the face of peritonitis, the combination of peritonitis with doubtful circulation of the bowel impelled us to seek another solution in this particular infant. The Mikulicz enterostomy seemed most appealing.

The double barrel enterostomy was first devised by Bloch of Copenhagen and Paul of Liverpool in 1892. It was popularized by Mikulicz of Breslau at the turn of the century and was widely used by Rankin in this country. Recent generations of surgeons have all but forgotten this procedure which has given way to primary resection and anastomosis both in adults and children. However, under certain circumstances, the Mikulicz procedure is of great value and may be lifesaving. The operation is widely used in pediatric patients by Gross (5) whose indications are: meconium ileus; congenital obstruction with marked disparity in size of bowel lumens; intraabdominal catastrophes requiring intestinal resection; doubtful viability of intestine.

The Mikulicz procedure has several

distinct advantages over a primary anastomosis:

1. The operating time is considerably shortened and therefore better tolerated by a desperately sick infant.

2. It affords rapid decompression of the intestine.

3. It is safer than risking an anastomosis in the face of frank peritonitis; even though an anastomosis is patent without leak, its function may be capricious and the infant may be deprived of much needed alimentary nutriment for weeks at a time. Many such babies wither away and succumb to aspiration pneumonia.

4. The procedure permits visualization of the ends of the bowel in cases of doubtful viability at the time of surgery.

There are also disadvantages to the Mikulicz procedure. Besides the fact that it is a multistage procedure with increased hospitalization, there are complications inherent in this operation which include: inadequate crushing of the spur with subsequent stenosis after closure of the enterostomy; perforation of the bowel or fistula formation if the crushing clamp damages the intestine deep to the point of approximation of the bowel loops; abscesses and skin breakdown; evisceration, prolapse or retraction of the stoma. Careful suturing of the bowel to the peritoneum and fascia of the wound is an important help toward avoidance of evisceration.

The metal umbilical clips which are applied to occlude the stoma permit some sealing of the wound before the gastrointestinal contents are allowed to issue forth (6). A gas-

trostomy is of utmost importance in every newborn baby who undergoes major abdominal surgery. Nasal irritation is avoided and the chance for aspiration is lessened. The tube is initially used for decompression and later it may be used for the early feedings.

In 1957 a Mikulicz procedure was employed in a child with gangrenous intussusception combined with barium peritonitis who was the first to survive this combination of circumstances (7). No particular problem of electrolyte or fluid losses were noted at that time nor were there any problems with the case herein reported. Gross (5), in his series of 196 infants and children who had Mikulicz resections, has seldom seen uncontrollable fluid and electrolyte losses; he believes that the fear of using enterostomy in infants is unwarranted. The spur crushing clamp may be applied between the second and the fifth day; it may even be applied in the operating room immediately after surgery if necessary. The spur usually sloughs away in 4 to 6 days. Closure of the ileostomy is performed after the peritonitis is under control and the wound is healed.

SUMMARY. Neonatal peritonitis is highly lethal, particularly when it is secondary to ischemic necrosis of the bowel. A case in which a peritoneal band compressed the superior mesenteric vessels is reported. The etiology and the use of the Mikulicz enterostomy is discussed.

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CASE NO. 6

Benign Esophageal Stenosis

Benign esophageal stenosis frequently occurs as a result of long-standing symptomatic hiatus hernia with esophageal regurgitation of acid peptic products (1-5). The treatment of the dysphagia associated with esophageal stenosis is a subject of controversy in the literature and ranges from more simple forms of bouginage to very complicated surgical procedures (6-16). The case presented is one where the patient developed esophageal stenosis secondary to a hiatus hernia, and was treated by a variety of means with ultimate success.

CASE HISTORY. This was the first Mount Sinai Hospital admission of a 42-year-old white male who entered with a chief com-

plaint of dysphagia and heartburn of fourteen months' duration. One year prior to this admission, he had noted the onset of substantial pain which was somewhat relieved by vomiting and which followed the ingestion of food. Often the patient was awakened during the night by a similar pain and obtained temporary relief with antacids. One month after the onset of these symptoms, a gastrointestinal series revealed a hiatus hernia of the sliding type and a stricture in the lower third of the esophagus. A repair of the hiatus hernia was performed at another hospital and, during this hospitalization, the patient lost thirty pounds. A recurrence of symptoms was noted within a few months after this initial surgery.

He consulted an otolaryngologist and was treated on three occasions with bouginage. Following each treatment, considerable relief was obtained for several months and he regained most of his lost weight. At the time of the first Mount Sinai Hospital admission, the patient was partaking only in a soft, bland diet. He did not smoke or drink. His past history was otherwise non-contributory. A gastrointestinal series performed during this admission (Fig 1) showed recurrence of a medium sized, sliding hiatus hernia. The esophagogastric junction was narrowed over a 5 cm segment and a 12 mm barium pill would not traverse the narrowed segment. The lower part of the esophagus was tapered. A definite ulceration or filling defect was not seen. The duodenal bulb was deformed consistent with the pyloroplasty performed at the time of the first hiatus hernia repair.

The patient was not anemic. During this hospitalization, the patient underwent a secondary repair of his hiatus hernia and vagotomy through a thoracoabdominal incision. The findings at operation included a one centimeter area stricture about 7 cm from the cardio-esophageal junction. The area of stricture was ulcerated and hardly admitted a fingertip. An attempt was made to enlarge the lumen at the stricture by closing the longitudinal esophageal incision in a transverse manner. The hiatus hernia was repaired by bringing the stomach below the diaphragm, tightening the crura, reconstituting the esophagogastric angle, and suturing the fundus of the stomach to the



Case No. 6, Fig. 1.

undersurface of the diaphragm. Postoperatively, the patient's course was complicated by non-specific toxic hepatitis; with supportive therapy, there was good recovery. The patient's bilirubin level returned to normal, his appetite increased, and he was discharged from the hospital during the third postoperative week. He was eating a soft diet, and was not complaining of heartburn or dysphagia.

Following discharge, the patient did not do well and was readmitted within two weeks. He had been unable to retain food for approximately four days. Esophagoscopy revealed a granulomatous suture line with exuberant squamous growth 37 cm from the upper incisor teeth. Two black silk sutures were removed through the esophagoscope and a 12 mm dilator was passed into the stomach without difficulty. Following dila-

tation, the patient improved and was again able to take solid food. He gained several pounds in the hospital and was discharged.

He was readmitted two months later with dysphagia for solid foods and recurrence of the esophageal stricture. Endoscopy revealed an esophageal ulceration 37 cm from the incisor teeth and the lumen was markedly narrowed at the esophagogastric junction. Several silk sutures were seen protruding into the lumen and were removed. The lumen was dilated up to 8.5 mm with a number 26 french bougie. Again, the patient improved and was able to tolerate solid food. He was once more discharged from the hospital, and did well for six months.

However, about one month prior to his fourth Mount Sinai Hospital admission, recurrent vomiting and heartburn was noted. He lost approximately ten pounds during this preadmission month, and could swallow only liquids. An upper gastrointestinal series (Fig 2) revealed a markedly narrowed lower third of esophagus. Above the narrowing there was a dilatation of the esophagus. Below this point of ballooning, there was a stricture measuring one centimeter in length. Barium only trickled through this area. The stomach appeared to be below the diaphragm.

Surgery was again recommended for the stenosis and it was decided that a resection of stricture and jejunal interposition would be performed. Esophagoscopy performed just before surgery showed a normal non-inflamed esophagus with a very tight stricture which would not permit the smallest bougie to be passed. At exploration, the esophagus above and stomach below the stricture appeared to be normal without mucosal inflammation. After resection of the esophagogastric junction and stricture, a ten-centimeter loop of jejunum, ten centimeters below the ligament of Trietz, was mobilized with its vascular pedicle and was led through the transverse mesocolon behind the stomach. This loop was anastomosed to the esophagus in two layers with a continuous inner chronic suture and outer interrupted silk in an isoperistaltic manner. The lower end was joined to the stomach similarly in two layers, and following the completion of these anastomoses the jejunal segment lay easily with one-half its length

lying intrathoracically without kinking, and anchored to the pleura by interrupted silk sutures. The distal jejunostomy was completed below the transverse mesocolon. The mesentery was closed and a gastrostomy tube was placed and the stomach sutured to the abdominal wall. Postoperative course was uncomplicated and the patient was discharged from the hospital, eating well, on the sixteenth postoperative day. Pathologic examination of the excised specimen showed a marked stricture at the gastroesophageal junction with extensive fibrosis and thickening of the submucosa and muscle coat and with chronic non-specific inflammation and foreign body granulomata of the esophagus and adjoining part of the stomach wall. A liver biopsy was without significant change except for focal areas of fibrosis.

During the three postoperative years, the patient continued to increase his dietary intake and his weight to a point where he now appears obese. At last follow-up, he had gained thirty-five pounds. There was no evidence of any heartburn or dysphagia, and gastrointestinal series (Fig 3) revealed passage of barium through the esophagus, the interposed loop and into the stomach. The esophago-jejunal anastomosis was located about 7.4 cm above the hiatus. The interposed segment was tortuous and there was no evidence of ulceration. Abdominal compression did not result in reflux into the interposed loop.

DISCUSSION. When the lower esophagus is subjected to the continuous exposure of acid-pepsin secretions regurgitating from the stomach, esophagitis with ulceration is likely to develop. With recurring esophagitis and ulceration, scar formation may progress to produce stenosis of the esophageal lumen (1-5).

The complications of regurgitative esophagitis are frequently seen with hiatus hernia (2, 4, 5). The presence of gastric mucosa above the diaphragm predisposes to the reflux of gastric secretions into the esophagus with resultant inflammation, ulceration, scarring and stricture.



Case No. 6, Fig. 2.

A considerable amount has been written about the mechanisms at the esophagogastric junction which normally prevent the reflux of gastric contents into the terminal esophagus. There is still disagreement amongst writers concerning the relative importance of these various mechanisms,

but in general there is agreement that the following factors play a role in maintaining the competence at the esophagogastric junction (17):

1. The position of the esophagogastric junction beneath the diaphragm.
2. The degree of snugness of



Case No. 6, Fig. 3.

the muscular crura at the esophageal hiatus around the esophagus.

3. The acute angle of insertion of the esophagus into the stomach; the 'angle of His.'

4. An intrinsic mechanism at the esophagogastric junction, possibly a function of the oblique fibers of the inner muscular layers of the stomach which loop around the insertion of the esophagus.

We believe that the most important factor in preventing reflux is the actual length of the intraabdominal esophagus. At the time of a hiatus

hernia repair, the surgeon should attempt to reconstitute as many of these factors as possible with particular emphasis on maintaining an intraabdominal esophagus. The difficulties in performing a satisfactory hiatal hernia repair are evident when one realizes the variant repairs which have been devised to treat this condition (18-20).

The described patient's primary hernia repair failed. The operative details of this repair are not available to us. No attempt was made to correct the stricture, and the continuing pathophysiological process resulted in almost complete obstruction

of his esophagus. When he was first seen at Mount Sinai Hospital with esophageal stenosis, there were several attempts at bougienage which offered the patient temporary relief. Bougienage should be the first approach to esophageal stenosis, and indeed, some physicians believe that almost all cases of esophageal stenosis can be corrected with either bougienage from above (1), or in those cases in which this is not possible, bougienage from below through an opened stomach at laparotomy (21). With a failure following his third bougienage, the patient was referred to the surgical service. It was felt at this time that some form of reconstructive surgery was necessary for this benign stricture and the following preoperative considerations were made:

1. Attempt to repair the hiatus hernia and enlarge the strictured area.

2. Transverse resection with end-to-end suture. This removal of the stricture would in no way affect the regurgitation of gastric contents into the esophagus, and the continuing devastating effects of regurgitation would continue with ultimate redevelopment of stricture.

3. Esophagogastrrectomy by drawing the stomach up into the thorax. This procedure combined with vagotomy and drainage procedure or with autrectomy, may alleviate the symptoms of esophageal stenosis (12, 13). However, it is a procedure which is often accompanied by gastric reflux. Though the absolute acid levels would be

lowered by the concomitant vagotomy and gastric procedures, there is still the possibility of recurrent esophagitis and stricture.

4. Esophagogastrostomy by means of a tube constructed from the major curvature of the stomach. This procedure has been used with success in treating strictures following failure of bougienage (15). Observations indicate that recurrent peptic esophagitis does not develop when the esophagus has been reconstructed by means of this reversed gastric tube.

5. An isolated interposed segment of small intestine or colon.

A new procedure has been recently added to the surgical armamentarium (6, 7) but at the time of this patient's surgery, was not described in the surgical literature. This procedure is one in which a fundie patch is used to enlarge the cardio-esophageal junction after making a longitudinal incision through the esophagus across the strictured area.

It was decided to attempt to repair the recurrent hiatus hernia and deal with the esophageal stricture by dilation from below or by some other means.

The failure of this procedure was most likely related to incomplete treatment of the stricture and to some degree of continuing reflux both of which shortly led to a recurrence of symptoms.

The subsequent selection of an interposed jejunal segment was made because of past success with that procedure, (9-11) and because it was thought that of all the choices open to us, it would be the most likely to

cure the patient's condition. The patient's relative youth also allowed for this extensive surgical procedure.

The advantages of this technique are the following: (16, 21)

[1] The jejunal segment retains the usual path of flow and allows for the excision of the diseased segment. It can also serve to elongate a shortened esophagus.

[2] It bridges the defect between esophagus and stomach with bowel whose mucosa has a high degree of resistance to acid-peptic digestion. Some authors feel that colonic mucosa serves this latter purpose better (23).

[3] It restores the sphincter function lost with excision of the cardia and allows for an intraabdominal segment of intestine proximal to the stomach. The disadvantages of this procedure include (8, 16, 21):

1. Requires extensive surgery and the three anastomoses make the possibility of a leak greater.

2. Vascular supply may be jeopardized especially in cases of a high esophago-jejunal anastomosis.

3. Possibility of ulceration, though not great, does exist when the jejunal segment is exposed to acid.

According to Robb (11), the potential problems associated with a jejunal interposition can be lessened by avoiding redundancy, taking great care with the vascular arcade supplying the segment, and by performing meticulous anastomoses. The surgeon should avoid having the jejunum pulled up into the chest by the negative intrathoracic pressure by placing

fixation sutures between the hiatus and the segment.

To date, the procedure has been successful in this patient, and the same high degree of success as described in the surgical literature (9-11, 16) and in our subsequent experience bears out its applicability in cases of lower esophageal stricture.

SUMMARY. A case of esophageal stenosis secondary to a sliding hiatus hernia is described. The use of an interposed jejunal segment appears to have succeeded in alleviating the condition where other methods have failed. A brief review of the methods of treatment and of the pathophysiology of reflux is included.

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RADIOLOGICAL NOTES

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CASE NO. 286

A 78 year old man complained of recurrent severe crampy abdominal pains of one week's duration. There had been nausea and constipation but no associated vomiting. The patient had not noted any rectal bleeding or melena. Two years before, an anterior resection had been performed for a sigmoid carcinoma. At this time, the patient was known to have nodular densities in both lungs, probably the result of hematogenous metastases. He was now referred for barium enema examination, to exclude the possibility of a recurrent malignancy within the colon. Preliminary examination of the abdomen revealed no distended gas-filled loops of bowel or abnormal calcification. In the splenic flexure, a smooth sharply demarcated homogenous soft tissue mass was noted to be outlined by air within the descending colon (Fig 1a). During the course of retrograde filling of the descending colon, a smooth sharp mass was encountered (Fig 1b). This represented an intraluminal tumor that had caused an intussusception into the distal limb of the splenic flexure. This was reduced and the tumor was noted to arise at the junction of the middle and distal thirds of the transverse colon (Fig 1c). The tumor was broad-based without ulceration or nodularity and had the typical appearance of a submucosal lipoma. The patient's abdominal cramps, which were undoubtedly related to the intussuscepting lipoma, were markedly improved after the barium enema.

DISCUSSION

Lipomas represent the most common benign tumors of the colon. More than half are located within the cecum and ascending colon (1). Although the majority of lipomas are asymptomatic, and are found accidentally during the course of a barium enema, some intussuscept, obstruct, and bleed (2). The roentgen findings are often typical and, as in the case presented, are sufficient to make a specific diagnosis. These include the finding of an intraluminal filling defect with sharp smooth contours and a broad base. During the act of filling of the colon with barium, or after evacuation, the mass is often seen to change in size and shape (3). This is probably related to its soft consistency.

Case Report: INTUSSUSCEPTING COLONIC LIPOMA.

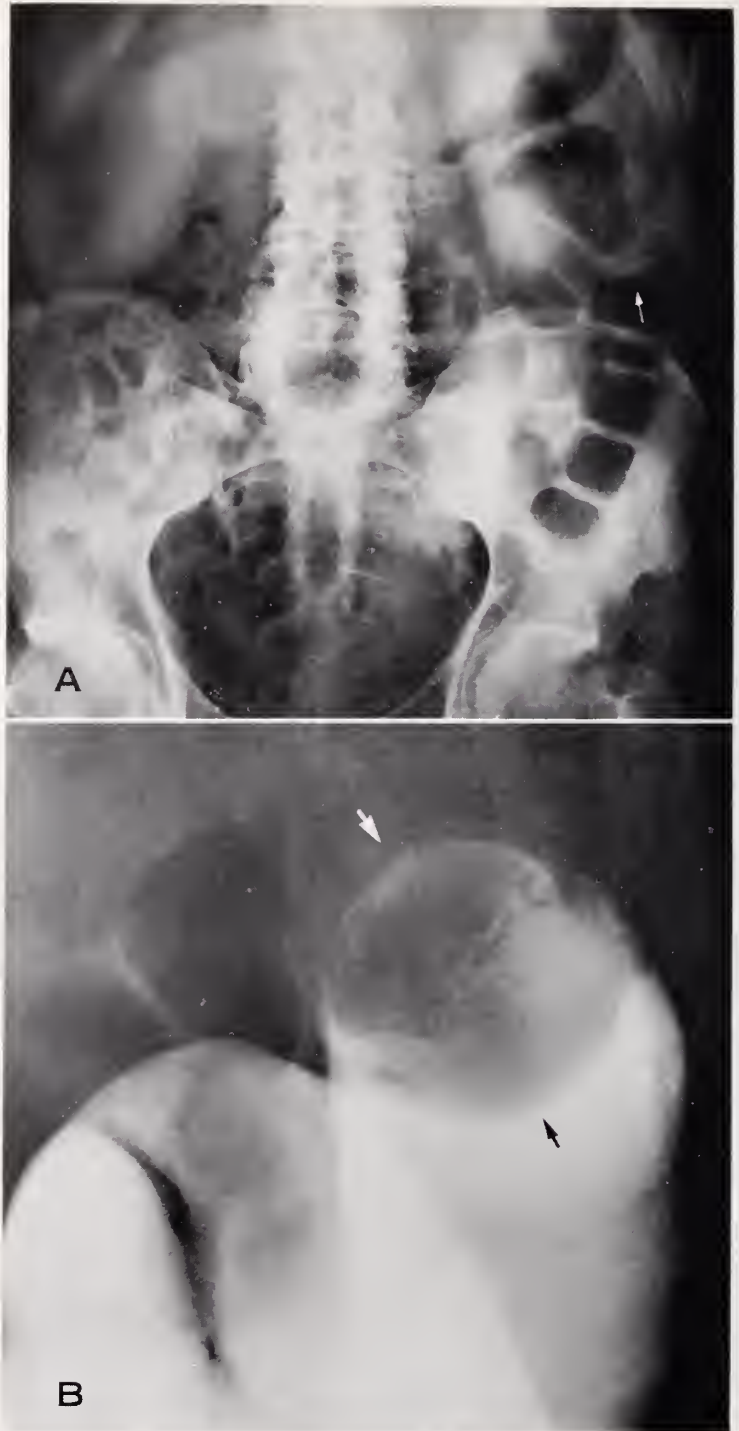
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Case 286, Fig. 1



Case 286, Fig. 1A. Anteroposterior view of abdomen reveals a smooth homogenous soft tissue mass outlined by air in region of the splenic flexure. Distally, air column in the descending colon outlines an exquisitely smooth, sharp outline to the mass (*arrow*). A small amount of air is noted in the splenic flexure itself outlining the superior border of the lesion. No further abnormalities are noted. No calcifications are seen within this mass.

Case 286, Fig. 1B. Spot film during the course of barium enema study reveals barium within sigmoid and descending colon. At splenic flexure, barium outlines a smooth, sharply demarcated mass (*lower arrow*). A small amount of barium outlines the periphery of the mass. Its proximal edge is also sharply delineated (*upper arrow*).

Case 286, Fig. 1C. Following barium enema examination, smoothly demarcated intraluminal mass is noted to be within distal portion of transverse colon (*arrow*). It has a broad base and has the typical appearance of a lipoma. During the course of fluoroscopy this lipoma, which was first encountered in the descending colon, was noted to be intussuscepting. The intussusception was reduced during the study.

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CASE NO. 287

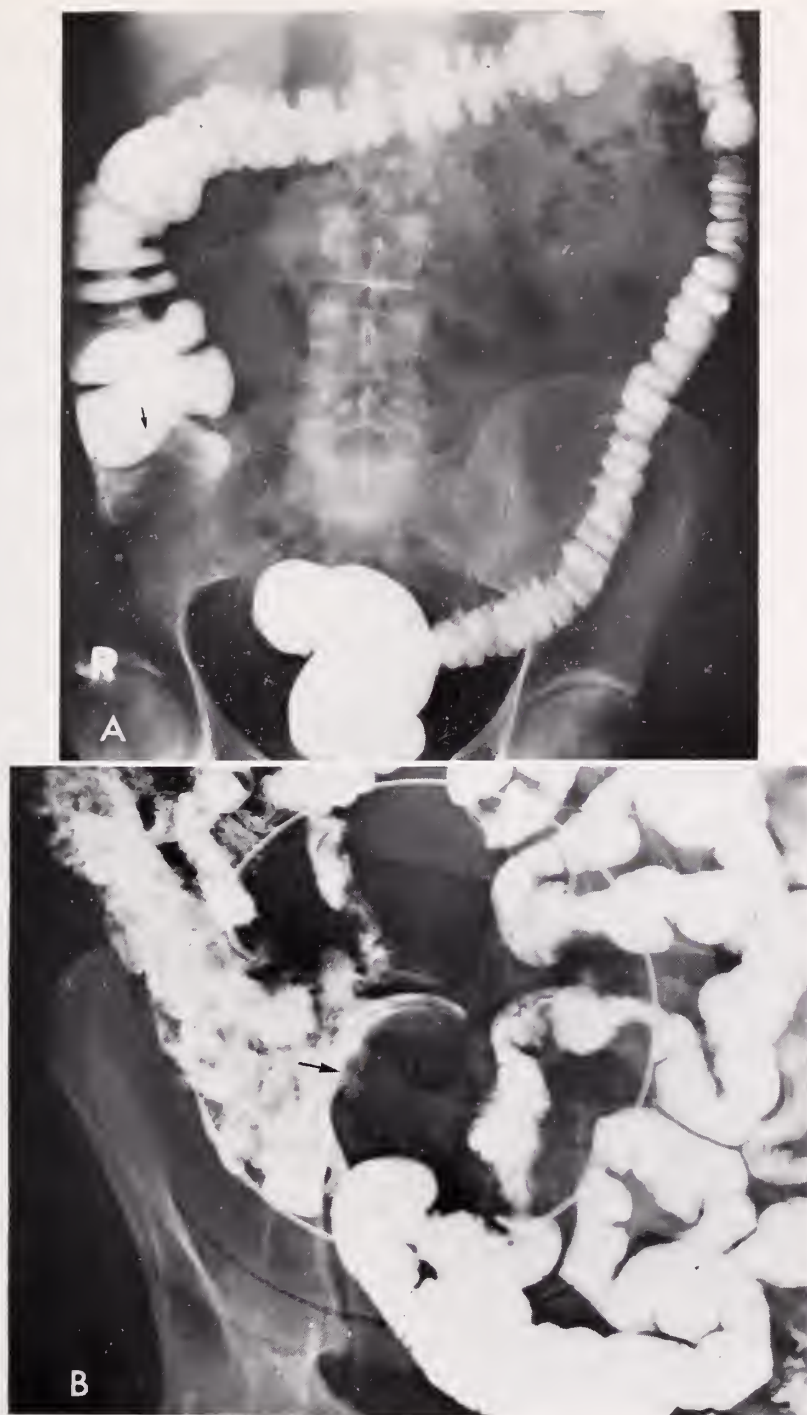
A 59 year old man was admitted to the hospital with a four week history of abdominal pains. During one such episode, the patient experienced hypotension and dizziness. There had been no anorexia, vomiting or abnormal stools. At the time of admission, vital signs were normal and physical examination was negative. The abdomen was soft and although some fullness and guarding were noted in the lower quadrants no discrete mass was palpated. Laboratory examinations were normal. Barium enema revealed a sharply demarcated filling defect indenting the inferior-medial aspect of the caput coli (Fig 1a). The contours of this broad-based mass were smooth and not abnormal calcifications of ulcerations were noted. There appeared to be a small degree of intussusception into the cecum. The appendix was not visualized, and the terminal ileum was not filled by reflux. A small bowel examination was then performed, and the lemon-sized smooth mass was again noted to be sharply delineated near the caput coli (Fig 1b). The terminal ileum was normal and the distal ileal loops were displaced medially and downwards by this mass. At exploratory laparotomy an 8 x 5 x 5 cm yellowish mass was found attached to the cecum. It was removed together with a portion of the caput coli. The patient made an uneventful recovery. The pathologic specimen revealed a markedly dilated appendix with thin translucent walls, which was filled with a mucoid gelatinous material.

DISCUSSION

Mucoceles of the appendix occur in approximately 0.2% of cases seen at autopsy (1). They are thought to result from an obstruction of the appendiceal lumen in the absence of living bacteria. The mucous secreted by the appendiceal mucosa thus accumulates behind the obstruction. A mucoid mass is then formed, surrounded by a paper-thin distended appendiceal wall. Radiologically, mucoceles present characteristically as sharply demarcated, broad-based filling defects invaginating into the cecal base. On occasion, as in the case presented, some degree of intussusception is noted. Sometimes a thin ring of

Case 287, Fig. 1A. Barium enema examination reveals sharply demarcated filling defect at caput coli (arrow). The borders of this mass are exquisitely sharp. There appears to be a small degree of intussusception. The appendix is not filled. Terminal ileum is also not filled. No abnormal calcifications are noted in region surrounding this mass.

Case 287, Fig. 1B. During the course of a small bowel study the lemon-sized mass is again noted to be in apposition with caput coli, producing an exquisitely sharply demarcated contour defect within base of cecum (arrow). It is also noted to displace small bowel loops medially and downward. Terminal ileum itself is normal.



Case 287, Fig. 1

calcification is seen within the wall of the mucocoele (2). The appendix is never filled. In the differential diagnosis, one has to include appendiceal abscess, inverted appendiceal stump, lipoma, and cecal carcinoma. Although abscesses occupy a similar location in respect to the caput coli, spasm and other functional changes are usually noted in the adjacent bowel loops. Lipomas, which often occur in the right side of the colon, are rare in the caput coli; typically, they change in shape with different degrees of colonic filling. Inverted appendiceal stumps are usually much smaller than mucocoeles. In cecal carcinoma, the mucosa is ulcerated and the surface of the lesion is irregular and nodular.

Case Report: MUCCOCELE OF APPENDIX.

ACKNOWLEDGMENT

The editors wish to thank Dr. Gerson J. Lesnick, Dr. Fred Stern, and Dr. Norman Simon for permission to publish this case.

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CASE NO. 288

A 48 year old woman was noted to have an abdominal mass during the course of a routine gynecological examination. There had been some left lower quadrant pains but no anorexia, weight loss, or abnormal bowel movements. Positive physical findings were limited to the abdomen, where a grapefruit-sized hard, non-tender mass was encountered to the left of the umbilicus. Laboratory examination revealed a microcytic hypochromic anemia with a hemoglobin value of 6 gm/100 cc and guaiac positive stools. Bone marrow examination was normal. In order to elucidate the nature of this mass an intravenous pyelogram was performed; this showed normal urinary tract. However, in the left upper quadrant there was an abnormal 3 x 6 cm collection of air, whose contours were irregular and scalloped (Fig 1a). This was later shown to correspond to a large irregular ulceration within a mass in the proximal jejunum (Fig 1b, 1c). Laparotomy revealed a 15 cm vascular ulcerated tu-

Case 288, Fig. 1A. Examination of abdomen in supine projection during the course of an intravenous pyelogram reveals 3 X 6 cm collection of air in left upper quadrant (between arrows). The contours of this air collection are irregular and somewhat scalloped. No recognizable normal bowel contours or mucosa are identifiable within this air collection. No soft tissue masses are identifiable.

Case 288, Fig. 1B. During the course of small bowel examination, a large amorphous barium patch is noted within jejunum. This represents an irregular ulceration measuring 8 cm diameter. The contours are irregularly scalloped. There appears to be a surrounding mass as the adjacent jejunal loops are somewhat separated from this ulcer. No evidence of proximal dilatation.



Case 288, Fig. 1



Case 288, Fig. 1C. In left posterior oblique projection, this large ulceration is noted to be situated anteriorly, plastered down against the anterior abdominal wall.

mor adherent to the anterior abdominal wall and arising from the jejunum 3 inches distal to the ligament of Treitz. A jejunal resection was performed with an end-to-end jejunojejunostomy. The patient made an uneventful recovery. Although the specimen showed local invasion into the abdominal wall, no mitoses or cell atypism was noted histologically. It was the pathologist's opinion that this represented a jejunal myoma.

DISCUSSION

(See discussion following Case 289).

Case Report: ULCERATING JEJUNAL MYOMA.

ACKNOWLEDGMENT

The editors wish to thank Dr. Arthur Sicular, Dr. Seymour Wimpfheimer, and Dr. Sheldon H. Calem for permission to publish this case.

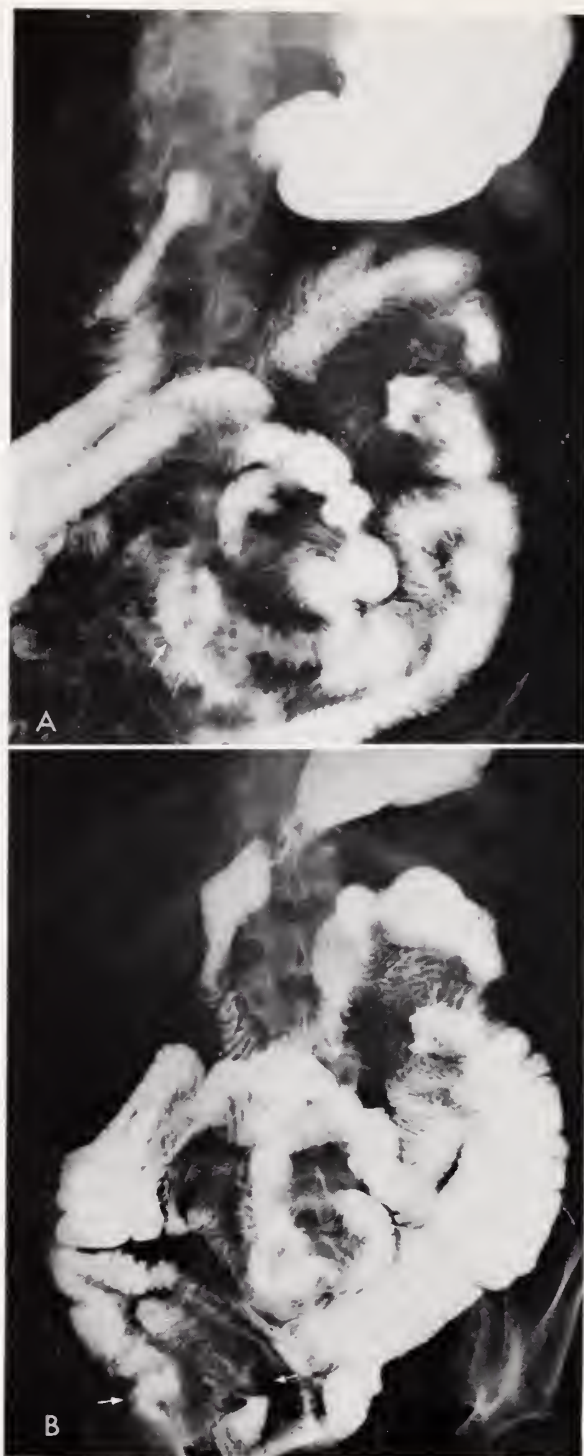
CASE NO. 289

A 39 year old man was well until 18 months prior to hospitalization, when he developed fever, fatigue, and neck masses. Biopsy of cervical lymph nodes revealed reticulum cell sarcoma. After local radiotherapy, these enlarged nodes disappeared completely and the patient was asymptomatic. Eight months prior to admission, he noted right flank pain; an obstruction to the lower portion of the right ureter was diagnosed. Pelvic radiation, together with systemic chemotherapy and steroids were then given. The patient again responded well and was asymptomatic until 4 months prior to hospitalization. Severe generalized abdominal pains were then noted without vomiting or melena. Physical examination revealed an acutely and chronically ill male with signs of a large left pleural effusion, numerous and large cervical lymph nodes, but no palpable abdominal masses or enlarged organs. Stool guaiac examinations were constantly positive and hemoglobin values ranged around 10 gm/100 cc. Sedimentation rate was 90 mm per hour. Barium meal examination revealed an ulcerating mass in the proximal jejunum (Fig 1a). The borders of this ulcer were irregular and nodular. The lesion displaced the surrounding small bowel without producing either angulation of the loops or obstruction. Two additional similar ulcerating mass lesions were noted—one in the distal jejunum and the other in the distal ileum (Fig 1b). In spite of these three large ulcerating lesions, there was no small bowel obstruction, shortening or fixation of large segments of bowel. The patient's condition deteriorated despite all supportive measures and he died.

DISCUSSION OF CASES 288 AND 289

After the stomach, the small intestine is the most frequent site of intestinal myomas. These can be intraluminal or extraluminal or a combination of these. Sarcomatous degeneration occurs in 20 to 25% of cases. Often, as in Case 288, the pathologist is unable to demonstrate cell atypism, mitoses, or widespread invasion, so that a pathologic diagnosis of myosarcoma cannot be made. However, these cases behave both roentgenologically and clinically as low grade sarcomas, with large irregular ulcerations, local invasion, and recurrences. Roentgenologically, the lesions of myosarcoma and lymphosarcoma may be identical. They present as large "aneurysmal" ulcerating masses continuous with the lumen of the bowel. The edges of the ulcer are irregular and nodular. There is usually no proximal small bowel obstruction and little or no shortening of the bowel is noted. When these small bowel lesions are multiple, the diagnosis is more likely to be lymphosarcoma or reticulum cell sarcoma. Myosarcoma and neurosarcoma are more likely to present as single lesions. Metastatic lesions to the small bowel from cellular or anaplastic carcinoma may entirely mimic the above findings, because of the lack of desmoplastic reaction. The most common primary sites are lung and breast. In these cases, there is however more evidence of small bowel obstruction. Metastatic melanomas to the small intestine may also produce similar lesions.

Case Report: RETICULUM CELL SARCOMA OF SMALL BOWEL.



Case 289, Fig. 1

ACKNOWLEDGMENT

The editors wish to thank Dr. Ezra M. Greenspan and Dr. Martin J. Weiner for permission to publish this case.

CASE NO. 290

A 45 year old woman was admitted to the hospital for evaluation of increasingly severe and frequent epigastric pains. These attacks started two years before admission and were typically colicky in nature, and unrelated to any particular foods or time of day. There was no radiation of this pain. No history of anorexia, weight loss or jaundice could be elicited. Physical examination revealed no abdominal masses or organ enlargement. No icterus was noted. Laboratory data revealed no significant abnormalities. The gall bladder could not be visualized on oral cholecystography. No right upper quadrant calcifications were identified. An intravenous cholangiogram was then performed which showed good visualization of the intrahepatic and common hepatic ducts; these were slightly dilated. There was a smooth arcuate extrinsic contour defect upon the lateral aspect of the common bile duct (Fig 1). The common bile duct was normal in course and caliber. At operation, the gall bladder was large and contained numerous small stones. There was some thickening at the neck of the gall bladder, but this was thought to be secondary to an impacted calculus within the proximal portion of the cystic duct. The common bile duct was not dilated. Cholecystectomy was performed and the patient made an uneventful recovery. The pathologic specimen revealed moderate generalized thickening of the gall bladder wall. High in the fundus, the mucosa was roughened. Near the neck of the organ, a flat 1.5 cm diameter hard grayish mass was seen infiltrating the wall of the gall bladder. Histologic study revealed an infiltrating adenocarcinoma of the gall bladder with squamous metaplasia.

Case Report: ADENOCARCINOMA OF GALL BLADDER.

ACKNOWLEDGMENT

The editors wish to thank Dr. Lawrence Essenson and Dr. Nathan Mintz for permission to publish this case.

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Case 289, Fig. 1A. Posteroanterior film during G.I. series reveals large amorphous patch of barium in proximal loops of jejunum which represents an ulcer crater with irregular nodular contours. A mass lesion surrounds this crater and displaces jejunal loops. A second similar large irregular ulceration is noted more distally within distal jejunum (arrow).

Case 289, Fig. 1B. Small bowel examination reveals a third large ulcerating lesion in distal ileum (between arrows). Again a large mass is associated with the irregular ulceration. Previously described jejunal lesions are again noted. No small bowel obstruction is noted.



Case 290, Fig. 1. During the course of intravenous cholangiogram, the intrahepatic and common hepatic ducts are seen to be slightly but definitely dilated. They are normal in course and do not contain intraluminal filling defects. In the proximal portion of common bile duct, near the expected entry of the cystic duct, there is a shallow smooth arcuate contour defect upon its lateral aspect (*arrow*). Distally, the common bile duct is entirely normal. There is contrast medium within the lumen of the descending duodenum.

The Membrane Lung Its Excuse, Present Status, and Promise

E. CONVERSE PEIRCE II, M.D.

THE EXCUSE

Although the concept of extracorporeal circulation is more than 150 years old (1), its use as an aid to open-heart surgery was not suggested until 1937 when Gibbon first reported his experiments with a rotating drum "oxygenator" (2). Dennis and his group were the first to undertake an actual clinical case (3). This was in 1950, and by 1955 Lillehei et al (4), Kirklin et al (5), and others were well on their way toward large series. At the present time many thousands of open-heart operations are performed every year. Although a variety of extracorporeal gas exchange devices are used, almost none of the surgeons employ membrane lungs. Since a reasonably practical membrane lung was described by Clowes, Hopkins, and Neville and used clinically as early as 1956 (6-8), one might well ask, "If the membrane lung has gained no significant popularity, why bother with it?"

The membrane lung is worth considerable effort because, of all the devices so far described, it is the least traumatic to blood (9-12). All artificial gas exchange devices, commonly miscalled "oxygenators," function by providing a broad area of blood in one phase to exchange with gas in a second phase. The membrane lung differs fundamentally in having a thin layer of plastic interposed between the blood and the gas. Refinements in pumps, tubing, cannulas, etc. have gradually reduced traumatic pressure, cavitation, jet, and shear forces that in early days resulted in gross hemolysis. There remain, however, the surface forces between the blood and the materials from which the machines are constructed. The areas of blood exposed to such materials are relatively small, fortunately, and there has been steady improvement in the type of material used. In general, trauma from non-wettable materials is probably related to surface free energy (Fig 1). In non-membrane devices, a much larger surface is exposed directly to the gas phase and the surface forces are strong, at least three to four times the magnitude of the forces between the blood and the materials of the circuit. Quantitatively, therefore, the forces between blood and raw gas are the most important forces in a properly constructed extracorporeal circuit. The interposition of a membrane, although it does not eliminate surface forces, reduces them greatly. The most satisfactory material is apparently a suitable form of silicone "rubber." *

Departments of Surgery and Physiology, Emory University School of Medicine, Atlanta, Georgia. Presented at the Lillenthal Memorial Lecture, February 19, 1966, Mount Sinai Hospital, New York.

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* Includes medical grade Silastic®, Dow Corning, and methyl silicone, General Electric.

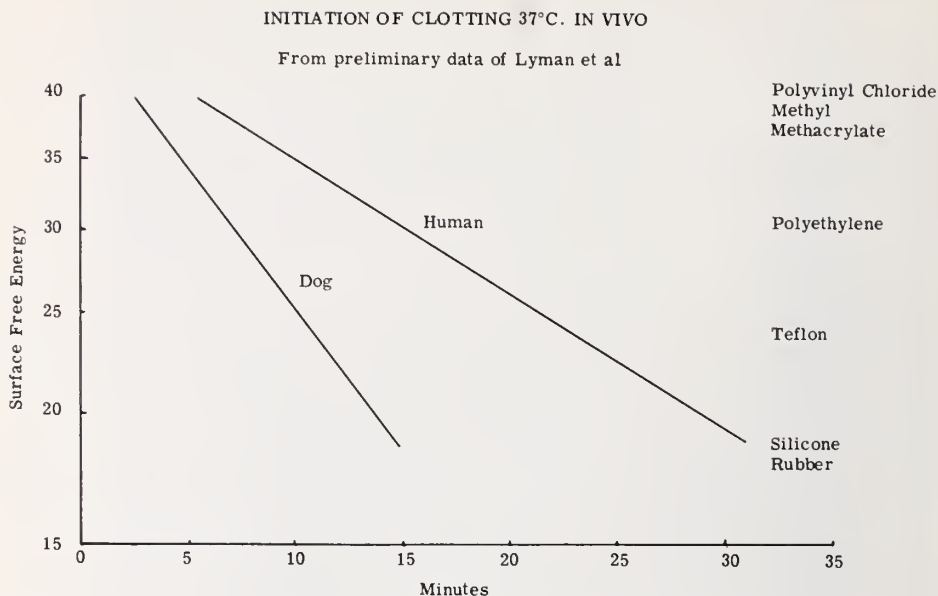


FIG. 1. The rapidity with which blood clotting is initiated is related to the surface free energy of various synthetic polymers. Energy units are in ergs per square centimeter or "critical" surface tension in dynes per centimeter (Lyman (72)). Temperature 37°C.

Traumatic forces may produce obvious hemolysis and damage to other formed elements, but these changes are not as important as denaturation of the plasma proteins. All soluble proteins are globular or ellipsoidal in shape. The surface forces at the blood-gas interface are sufficient to elongate the proteins with disruption of interchain cross-linkages including disulfide bonds (11, 13). The resulting elongation (and asymmetry) reduces solubility and may be accompanied by changes in biological activity and optical properties while changes in the free groups cause differences in reactivity (13).

Elongated lipoproteins may be separated from their fat molecules and these may then coalesce to form lipid aggregates, large enough to cause emboli. Fat embolization contributing to the death of the patient has been found in clinical cases where perfusion is prolonged. Owens, Adams, and Scott, in evaluating this clinical finding, demonstrated that two hours of controlled perfusion with a filming "oxygenator" regularly produced widespread fat embolization (Fig 2) (12). A Teflon* membrane lung used at the same flow with the same pump and circuit produced no evidence of fat aggregation or embolization.

The free groups on the elongated proteins may result in attachment to red cells, forming sticky coatings, and promoting hemagglutination, "sludging," and capillary obstruction. Proteinoid precipitates and emboli have frequently been reported in extracorporeal circulations. Figure 3 shows one mechanism

* Tetrafluoroethylene Dupont (Fluorfilm®, Dilectrix Corporation, Farmingdale, New York).

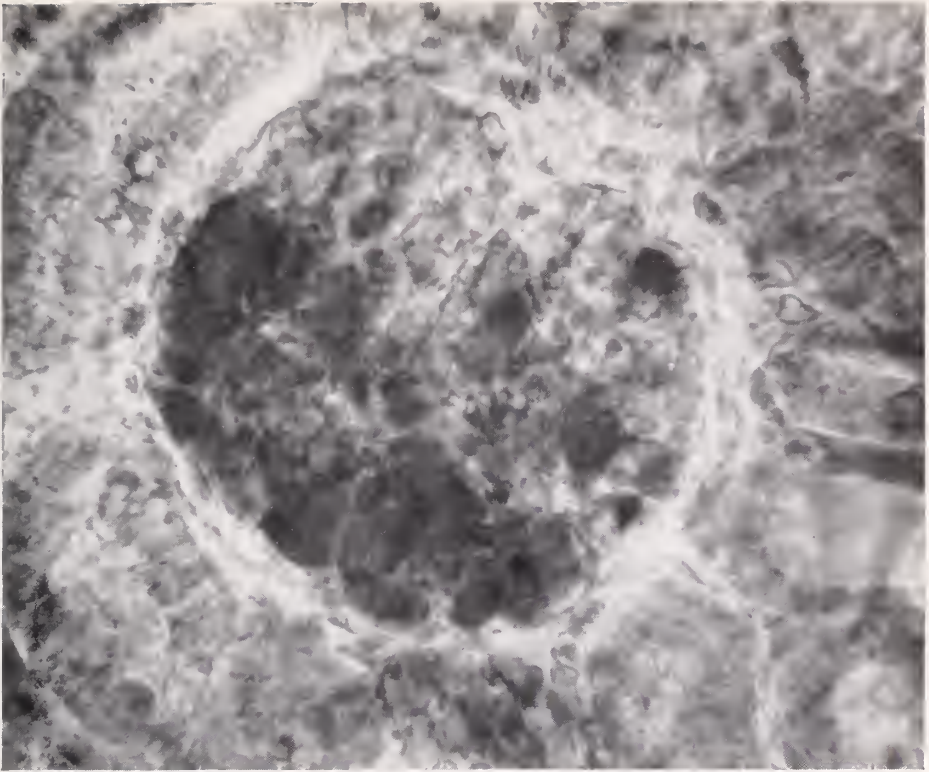


FIG. 2. Fat emboli filling glomerular vessels are shown in a kidney taken from an animal perfused for two hours with a screen "oxygenator." Courtesy of Dr. Guy Owens, Roswell Park Memorial Institute, Buffalo, New York.

FIG. 3. A soluble amorphous polypeptide shows structural rearrangement when elongated. The regular helix formed is insoluble. Redrawn from Zimm (73).

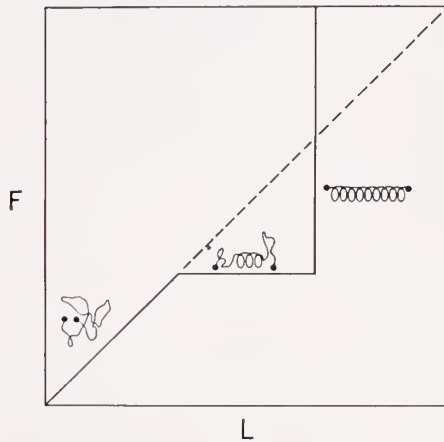


TABLE I*

Comparison of Plasma Denaturation by Membrane and Non-membrane Lungs

	Non-membrane Disc, Bubble, Screen 38 experiments	Membrane 0.5 mil, Teflon 7 experiments
In Vitro:		
Increased viscosity.....	100%	14%
Protein denaturation.....	Marked	Slight
Increased turbidity.....	Marked	Slight
Chylomicron aggregation.....	Marked	None
Simulation of incompatible cross match	60%	None
Amorphous red cell coating.....	75-100%	50-90%
In Vivo:†		
Conjunctival sludging.....	Marked	Slight
Capillary occlusions.....	50-60%	0-2%
Shock.....	25%	None
Decerebration.....	40%	None
Death.....	16%	None

* Lee et al 1961 (10).

† 10-12 ml/Kg of 16 hour circulated plasma infused in dogs.

where stretching of a polypeptide can cause rearrangement to a more stable but less soluble form.

Lee et al in an excellent comparative study, performed with plasma to eliminate the confusion of hemolysis and cellular trauma, showed that non-membrane devices produce severe protein denaturation both in vitro and in vivo (Table I) (10). Marked changes in viscosity, solubility, turbidity, and coating of red cells was shown routinely for the disc, bubble, and screen "oxygenators." In animal studies, the injected plasma produced marked sludging in conjunctival vessels with severe capillary occlusion, and in some dogs shock, decerebration, and death. All of the in vivo changes were much less marked in Teflon membrane experiments. Some changes were produced but were much less important biologically. These could probably be still further reduced by using silicone membranes. Although there are still some skeptics, much of this work has been confirmed by other investigators (9, 12).

A secondary benefit of utilizing a membrane to separate blood and gas results from the presence of two stable phases, so well separated physically that lung volume may be controlled automatically. The compliance of the membrane lung depends mainly on the material from which the membrane supports are constructed, but in a typical application, shown in Figure 4, lung volume changes only slightly with flow rate despite relatively large changes in perfusion pressure (14). To provide a completely stable blood volume, it is only necessary to circulate the blood through the lung at a constant rate, slightly higher than the maximum rate desired for arterial flow. A schematic membrane lung circuit is shown in Figure 5. The lung is properly represented

FIG. 4. Lung volume changes relatively slowly with blood flow. It is increased only about 25 per cent when blood flow is raised from 200 to 400 ml per kilogram per minute. The membrane lung is consequently very useful in maintaining constant patient volume.

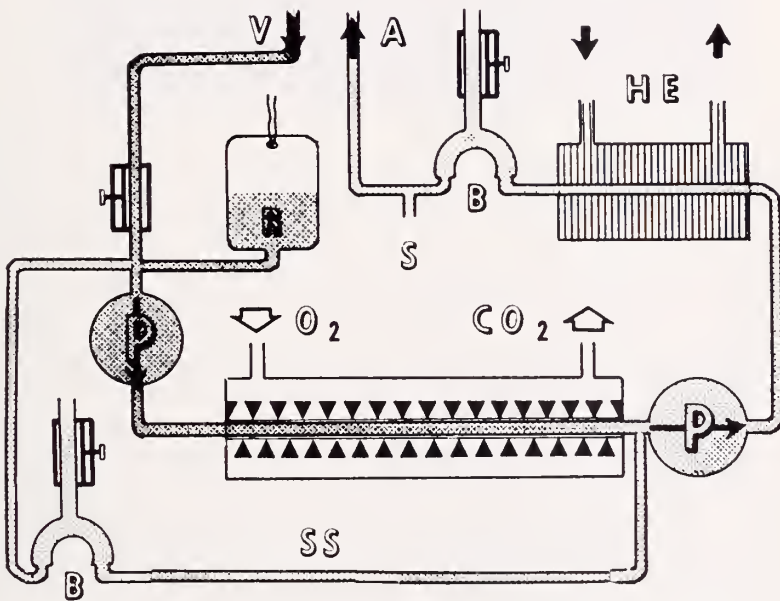
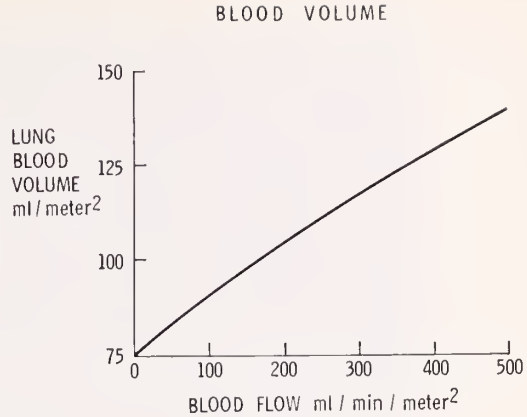


FIG. 5. Diagrammatic representation of closed extracorporeal perfusion circuit incorporating a membrane lung. Venous blood (V) drains into reservoir (R) regulated by a screw clamp. Blood is pumped by venous pump (P) through the membrane lung where oxygen uptake and carbon dioxide release take place. When arterial pump (P) is not running, blood recirculates through shunt line (SS) and bubble trap (B). To maintain a constant blood volume, the rate of circulation through the lung is maintained at the same speed, usually higher than the maximum to be pumped by the arterial pump. The arterial line consists of arterial pump (P), heat exchanger (HE), bubble trap (B), sampling port (S), and arterial line (A).

without any controls and operates with as little adjustment as the heat exchanger or the pumps.

The membrane lung thus needs no excuse since, by reducing trauma, it provides better biological security in prolonged perfusions. Also, because it permits close blood volume control, it is especially suitable in small subjects

TABLE II
Human Lung

Functions
Oxygenate blood
Eliminate Carbon Dioxide
Maintain pH
Unit
Alveolus
Air Sac
Membrane
Capillaries
Range
Ventilation: 5 to 100 liters/min
Blood Flow: 3 to 30 liters/min
Gas Exchange: 200 to 2400 ml/min

and where "fail-safe" features are important, as in prolonged assisted circulation.

PRESENT STATUS

The membrane lung may instructively be compared to the natural lung which provides not only for proper oxygenation but also for carbon dioxide elimination and thereby for maintenance of proper acid-base balance. The normal lung unit consists of air sac, membrane, and capillary, comprising together the alveolus. Looking at the range of function provided by the natural lung (Table II) will make it apparent that provision for basal function, which is all we presently aspire to, is very far from duplicating the natural lung. Ten to 20 times the basal capacity would be required to duplicate this marvelous device. Some of the dimensions in the human lung are illustrated in Figure 6. The red cell is approximately seven microns in diameter so that the membrane, composed of endothelial cell, alveolar capillary cell, two basement membranes, and an intermembranous space is perhaps two to three microns or about 0.1 mil thick. An important feature is that the human membrane is self healing. On the other hand, an advantage of the synthetic membranes is that they are very much stronger so that lungs highly resistant to pulmonary edema can be constructed.

Only two membrane materials, namely Teflon and silicone, are worth considering in a membrane lung at the present time though others have been tried (6, 8, 15-20). A variety of diffusion methods have been used to study membrane permeability to gases (17, 21-27). Table III shows data obtained using the membrane lung as a diffusion chamber (43). A well supported membrane area of about 625 cm² is provided. This is sufficiently large to permit diffusion to be measured with a recording spirometer. Teflon is available as thin as 1/8th mil but such thin membranes have not been useful in a sandwich

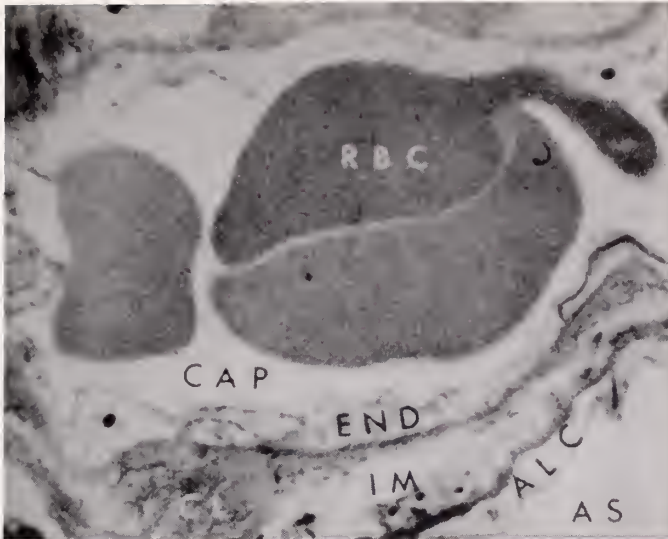


FIG. 6. Human pulmonary alveolus (AS), alveolar membrane, and alveolar capillary (CAP) containing red cells (RBC). The alveolar wall consists of endothelium (END), intermembranous space (IM), alveolar lining cell (ALC), basement membranes, and collagen (CL). From JAMA, March 21, 1964, Vol. 187, page 940, by permission. Courtesy of Divertie and Brown (74).

TABLE III
Diffusion Rates for Available Membranes 1966

	O ₂ (650 mm)	CO ₂ (40 mm)
Teflon 1/8 mil	200	32*
Silastic® 3 mil	300	80
Silicon 1 mil	1200	325

* In actual use this value may be exceeded.

Diffusion rates in milliliters per square meter per minute at available gradients.

From Galletti, Snider, and Silbert-Aidan (22).

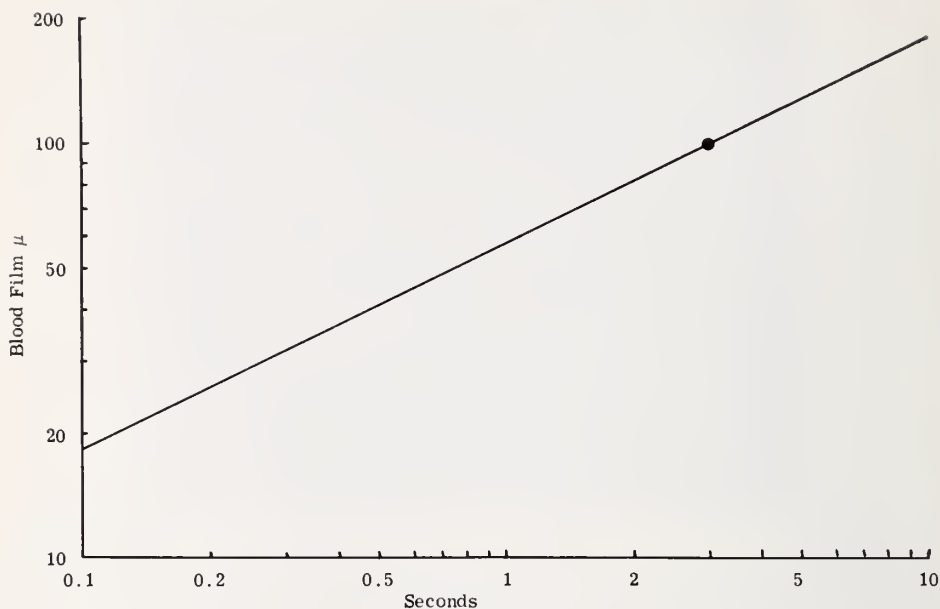
type lung although used by others in lungs of different design (29). Silicone membranes are available in quantity, as thin as 3 mils, reinforced with nylon or daeron mesh.* Recently a method of building up a reliable 1 mil membrane of methyl silicone by lamination has been developed (30).† This membrane is strong enough to be used without reinforcement.

In large measure, membrane permeability determines only carbon dioxide transfer while oxygen uptake is more specifically related to the design of the lung (23, 26, 31-32). The general principles governing membrane lung function may be seen well in the study of Teflon. This material varies in gas per-

* Dow Corning Corporation, Silastic®.

† N. R. Dibelius, General Electric Company, Schenectady, New York.

THEORETICAL TIME TO OXYGENATE 50% SATURATED BLOOD AT 37°C



From Data of Marx et al.

FIG. 7. A blood film of 100 microns may theoretically be brought from 50 per cent to full saturation in about three seconds. Thicker films require disproportionately much longer oxygenating times. Thinner films require excessive flow rates per unit area of membrane. This results in prohibitive perfusion pressures unless the flow path is made very short. Thick films thus require increasingly vigorous agitation while the use of thin films and membranes of high gas diffusion rate can be useful only with very refined lung design. (Courtesy Trans Amer Soc Artif Intern Organs (25).)

meability with its density (26). Clinical Teflon membranes are of relatively low density and have a carbon dioxide permeability of about 2.6 times that of oxygen. Because of limitations in the tolerable partial pressure of carbon dioxide in blood, the carbon dioxide driving pressure may not exceed 40 to 50 mm Hg and, if there is any non-respiratory acidosis, should be less. For this reason, a Teflon lung designed for full respiratory support must have a membrane area sufficient for the needed carbon dioxide diffusion (26, 32). Fortunately, carbon dioxide diffuses through blood about 30 times more rapidly than does oxygen. In consequence, liquid phase diffusion provides little barrier to the egress of carbon dioxide and almost the full membrane permeability may be utilized. Oxygen diffusion into blood, on the other hand, is markedly dependent on the character of the blood film (26, 32). The diffusion of oxygen is not only limited by its relatively low solubility in plasma compared to that of carbon dioxide but also by the "sink" effect of desaturated red cells. Thus blood acts as a formidable barrier to the transfer of oxygen into any but the thinnest blood films. The rate of oxygenation of an unagitated film of blood already 50% saturated and exposed to oxygen on both sides is shown in Figure 7. Very small differences in blood film thickness result in relatively large

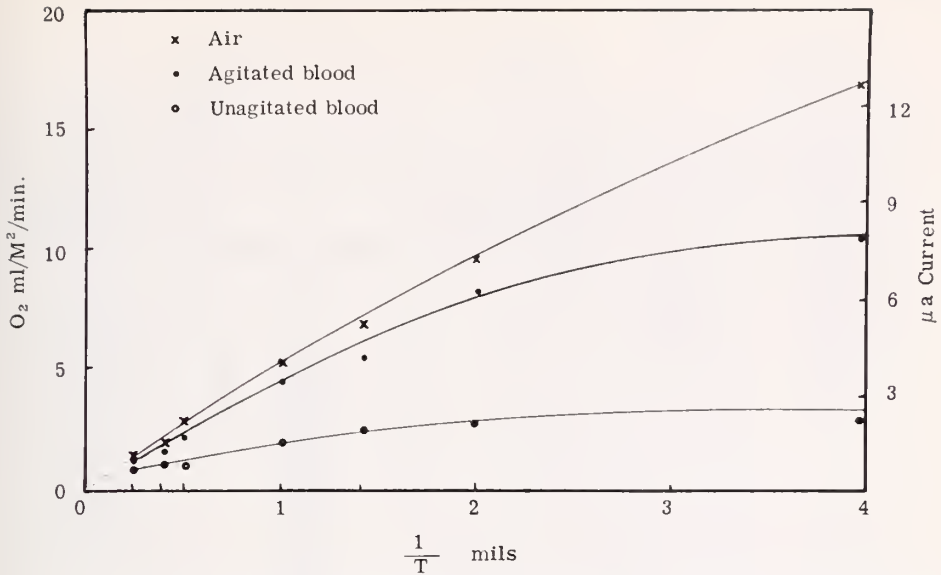


FIG. 8. The effect of agitation on diffusion of oxygen into a blood film is illustrated. Blood was equilibrated with air and the diffusion of oxygen from the blood to a sensing platinum polarographic electrode was measured. The electrode had an area of 3.14 mm^2 and the measured current flow was proportional to oxygen diffusion. When the blood was not agitated, diffusion was low and only slightly dependent on membrane permeability (thickness). With agitation, oxygen diffusion approached the values found for the electrode in air. Agitation, however, was insufficient to permit full utilization of the diffusion capacity of the $1/4$ mil ($1/T = 4$) Teflon membrane.

changes in the rate of oxygenation. As shown in Figure 8, the slow diffusion of oxygen into the blood film may be overcome to some extent by agitation (26). In this example, agitation of blood increases transfer of oxygen through $1/4$ mil Teflon membrane covering a Clark oxygen electrode (33) by about four-fold. Within the lung described in this paper agitation has been limited to breaking up streamlining patterns. This alone has been helpful in increasing oxygenation. In the absence of agitation, oxygenation in a membrane lung using Teflon is dependent entirely on the geometry of the blood film (26, 32). It may be enhanced by pressurizing the lung but this does not increase carbon dioxide exchange (34).

The modified Clowes lung (Fig 9), which has now been studied extensively, consists of a holder for alternating pairs of membranes containing the blood films and for supporting mats which contain manifolds for blood and gas (9, 12, 35-42). A pneumatic shim regulates blood film thickness by providing a controllable and even compression of the blood film between the supporting mats.* The scheme for blood and gas flow is relatively simple, and easier to understand after actual experience with the devices (Fig 10). Venous blood enters from a blood manifold. It is forced between the membranes along one

* Original pneumatic shim designed and built by Hardy Products Company, Decatur, Georgia.

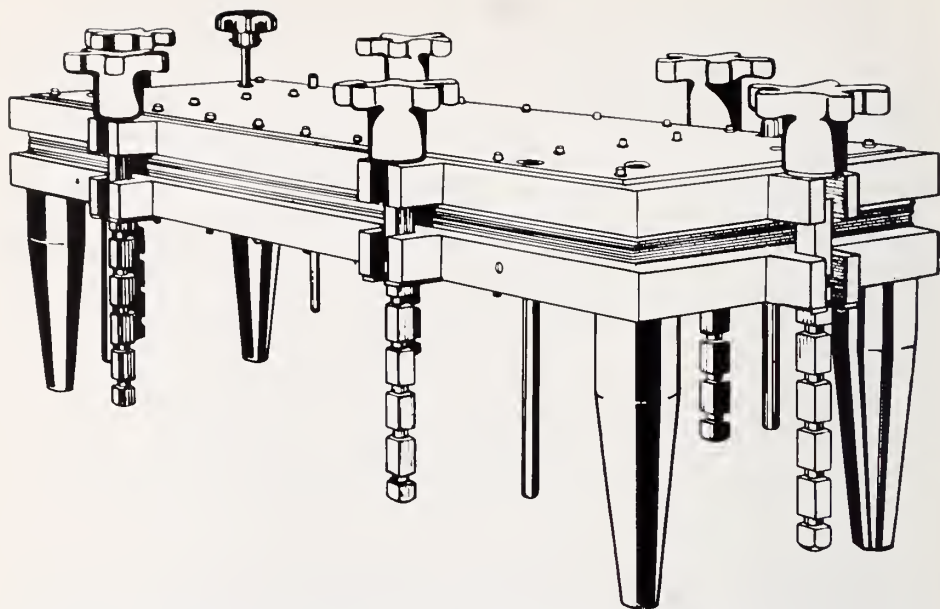


FIG. 9. Lung frame. This is made of cast aluminum and measures approximately 26 inches in length. When used with the insert jigs shown in Figure 12, the frame need not be sterilized.

side of the supporting mat, across the short dimension of the mat cone field, along the other side of the mat, and out a corresponding blood manifold at the other end. In the manifolds, the blood is distributed by Teflon discs containing small radial holes. These are stacked one over another and leakage between them is prevented by compression provided by a thrust bearing in the upper lung frame. A separate manifold is provided for the distribution of the gas to the other side of the membrane. The support mats have a central functional area of five inches by 20 inches. The two layers of supported membrane, comprising a single functional layer with one blood film, are approximately 0.125 square meters. The mats and membranes are sealed laterally by compression clamps on the periphery of the lung frame. Thus, there are three separate adjustments in the lung: (1) clamps for peripheral sealing to prevent leakage, (2) thrust bearings to seal the membranes and distribution discs, and (3) a pneumatic shim or bladder, of the same area as the functional part of the support mats, to provide uniform pressure over the area of the cone points thus regulating the thickness of the blood film (Fig 11).

The device is tested pneumatically before use. This has eliminated problems of leakage noted by others (28). Steam, ethylene oxide, or bactericidal fluid may be satisfactorily used for sterilization. The use of light metal assembly jigs simplifies gas or steam sterilization and storage (Fig 12).

The lung has been carefully evaluated in a steady state circuit containing an homologous lung to desaturate blood and add carbon dioxide and a heat exchanger to control temperature (Fig 13) (25-26). The unit to be tested is

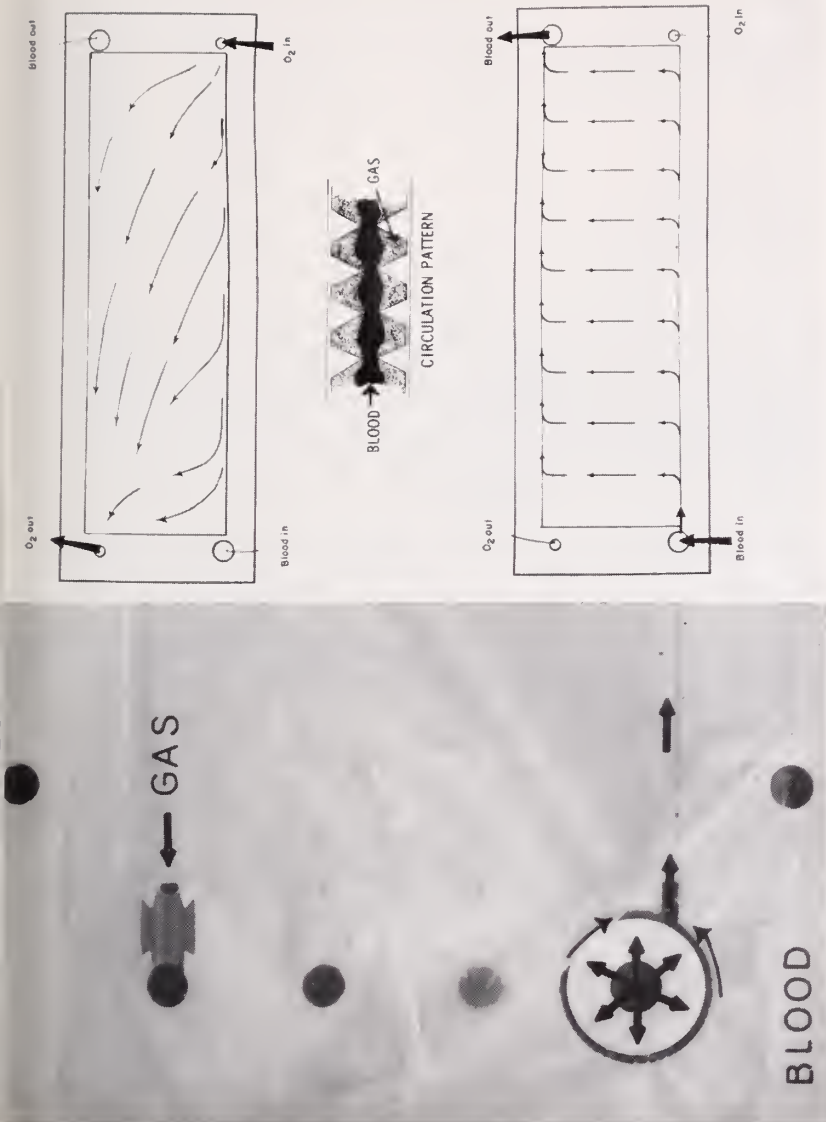


FIG. 10. Blood and gas flow are illustrated by reference to a single pair of membranes and support mats. Blood from the inlet manifold is directed between the membranes by six channels in the Teflon distribution disc. It proceeds the length of the membrane directed by the longitudinal groove in support mat. Blood then passes uniformly across the short dimension of the support mat and is again directed by the longitudinal distribution channel to the blood manifold diagonally opposite. Oxygen enters the space beneath and above the membrane blood envelope formed by the supporting cone points. It is roughly directed across the path followed by the blood. The gas volume flow is sufficient so that the direction of gas flow is relatively unimportant. A shows an actual photograph of an end of a mat, two layers of Teflon and a distribution disc. B, indicates flow pattern for gas (*above*) and blood (*below*). The relationships of blood, membranes, oxygen, and cones of the supporting mat are shown in the small central figure. Note how the membrane deforms into the cone field to form small preferential channels or capillaries.

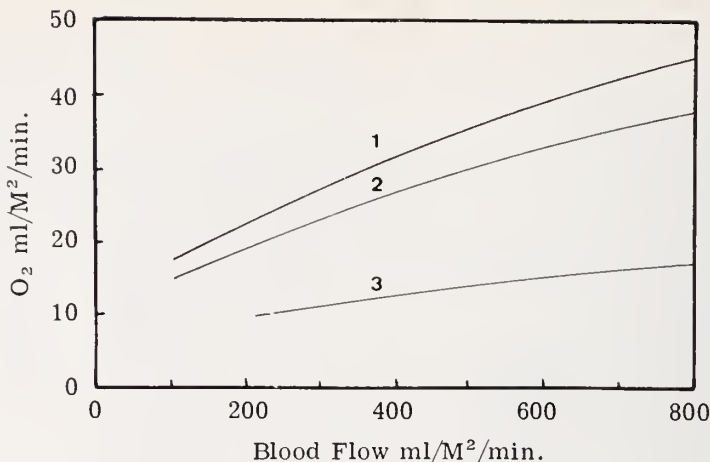


FIG. 11. The use of a pneumatic shim limits the volume and irregularities of the blood film and consequently greatly enhances oxygen exchange. The approximate relationship between an unshimmed lung (3), a lung shimmed to 150 mm Hg (2), and a lung maximally shimmed (1) is shown at a temperature of 37° C. The actual oxygen exchange varies also with the degree of saturation and oxygen capacity of the venous blood.

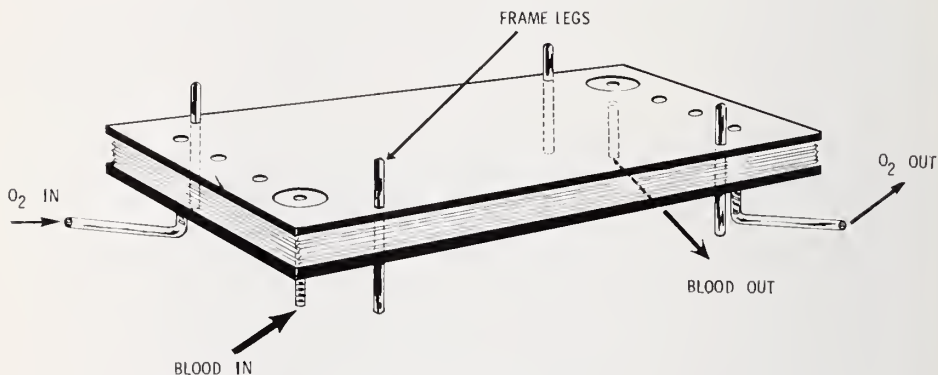


FIG. 12. The functional portion of the lung is now generally built on an insert frame or jig. This includes the fittings for blood, gas, and pneumatic shim. It is light enough so that the assembled lung units may be readily handled by a single person.

placed on a balance so that changes in volume may be noted. Inlet and outlet samples are taken for gas analysis and values are corrected for any temperature differential across the lung. A fixed outlet pressure is generally employed. This subtracted from the inlet pressure provides the perfusion pressure. The test circuit is run until a steady state is reached. Various parameters relating to lung function such as blood flow, gas flow, and the like may be varied quite readily and a full picture of the functional capacity of the lung may be obtained (Fig 14, 15). A variety of membrane supports, including the original stair-tread support of Clowes (8), a wire screen on perforated aluminum support (37), and the multiple cone support originally described by Leonard

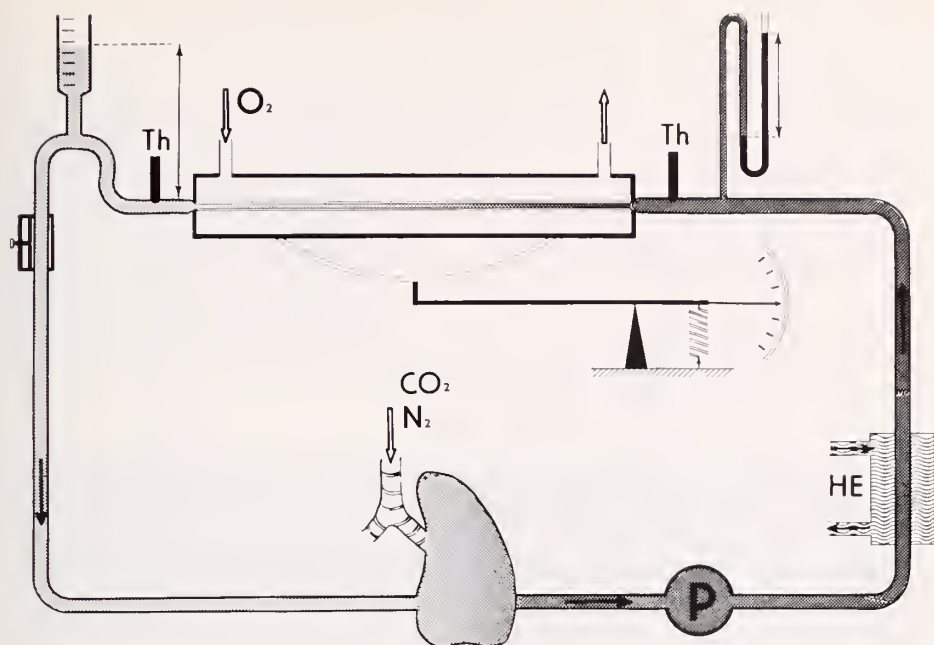
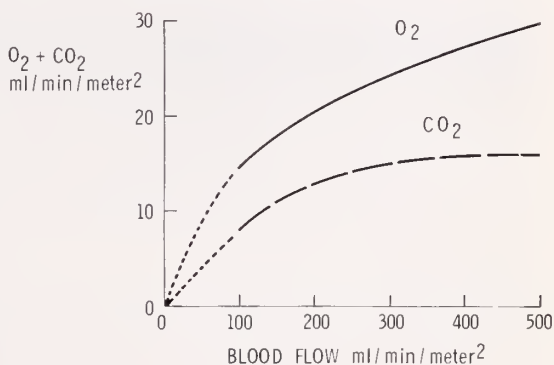


FIG. 13. The steady state circuit used commonly in lung evaluation is illustrated. The homologous lung desaturates the blood and adds carbon dioxide. The single pump (P) carries blood to the membrane lung through the heat exchanger (HE). Inflow pressure is measured by a mercury manometer and inlet and outlet temperature by thermistors (Th). The membrane lung rests on a scale so that changes in lung volume may be ascertained. The flow is determined intermittently by occluding the outflow line with the screw clamp below the calibrated open bubble trap. New membranes, variations in support mats, etc may readily be tested accurately (14).

GAS EXCHANGE

FIG. 14. Gas exchange at $37^\circ C$ is shown at various blood flows. Oxygenation, which is limited by the rate of diffusion of oxygen in the liquid phase, increases progressively since higher flow rates increase agitation. Carbon dioxide exchange is limited by membrane diffusion and is thus relatively constant. Data are for 0.5 mil Teflon.



and Bluemle (Fig 16) (43-45)* have been evaluated. The multiple cones provide uniform membrane support so that a pair of Teflon membranes form a network of functional capillaries. Oxygenation and, to a smaller extent,

* Obtainable from Dow Corning Corporation, Midland, Michigan.

LUNG PERFUSION PRESSURE

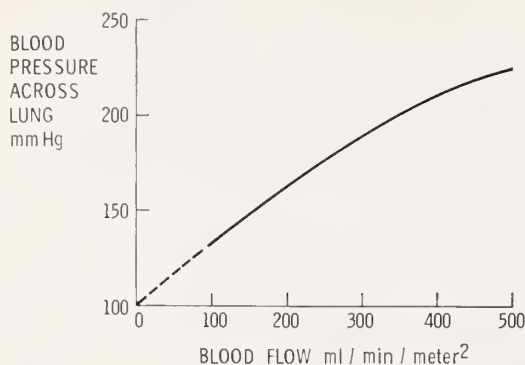


FIG. 15. The relationship between perfusion pressure and blood flow is illustrated for a slim pressure of approximately 150 mm Hg. Pressure increases less rapidly than flow but still becomes very high at flows exceeding 400 to 500 ml per square meter per minute. Data are for 0.5 mil Teflon. Much lower perfusion pressures at even higher flows are possible when silicone membranes are used with an internal screen support as illustrated in Figure 28.

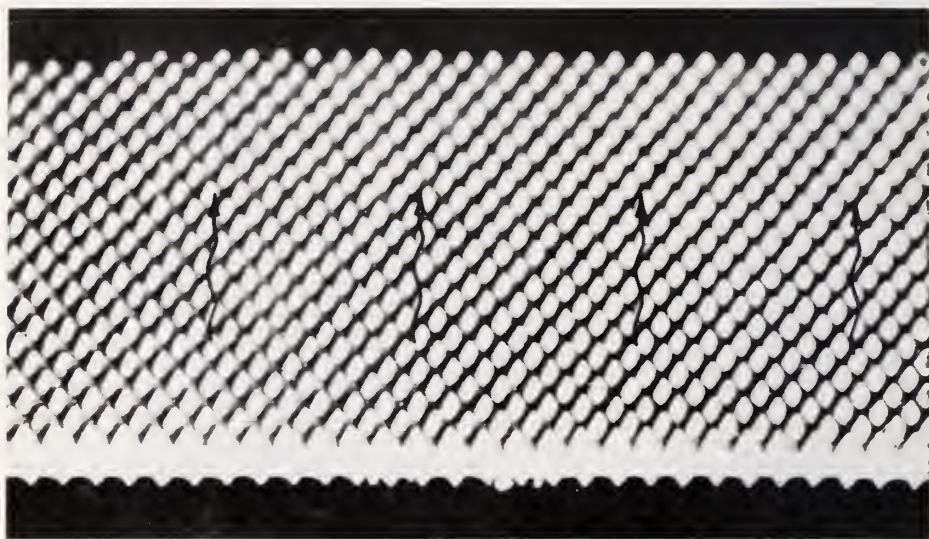


FIG. 16. Cross section of a small area of a support mat to show character of the multiple support pattern. The cones are approximately 30 mil high and spaced 30 to the inch. These support the membranes which enclose the blood film. The cones are staggered so that there is no straight path for blood across the cone point field. The direction of blood flow is shown by arrows ($\times 4$).

carbon dioxide elimination increase with increasing blood flow. For oxygen, this indicates that more rapid flows produce greater agitation of the blood. As the flow rate increases, oxygen transfer approaches the diffusion capacity of the membrane shown in gas-to-gas chamber studies. Even at low flows, carbon dioxide exchange is at the theoretical maximum, and as flow increases, this maximum is exceeded (14). A secure explanation is not available for this phenomenon but, in all probability, either membrane pores are enlarged or functional hydration of the membrane is increased as perfusion pressure rises. Either of these factors would be expected to increase carbon dioxide transfer.

Fig. 17. Gas exchange in the membrane lung for 0.5 mil Teflon at varying temperatures is illustrated. Oxygen exchange falls fairly rapidly since the blood film increases in thickness as the viscosity rises with falling temperature. Carbon dioxide exchange, however, is relatively unchanged with temperature since its egress from blood is principally related to membrane diffusion and for Teflon this varies little as the temperature changes. The balance of oxygen and carbon dioxide exchange is better in the cold lung.

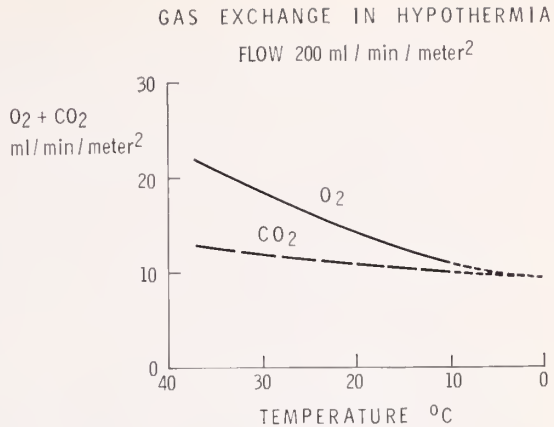


TABLE IV
Comparison of Membrane and Human Lung
0.5 mil Teflon 300 ml/minute flow

Gas	Human lung (basal)	Membrane lung
	Air	Oxygen
Average O ₂ gradient	45 mm. Hgb	650 mm. Hgb
Average CO ₂ gradient	3 mm. Hgb	45 mm. Hgb
DCO ₂ /DO ₂ * . . .	15	15
Blood film thickness . . .	0.01 mm.	0.16 mm.
Transit distance . . .	0.75 mm.	10 cm.
Transit time . . .	0.75 sec.	20 sec.
Blood flow/M ² /min.	25 ml.	300 ml.
Blood volume/M ² .	2.5 ml.	100 ml.
Total volume/M ² .	45 ml.	1250 ml.
O ₂ and CO ₂ /M ² /min.	2 ml.	20 ml.

* D = ml diffused per millimeter of mercury pressure per minute.

The Teflon membrane lung operates satisfactorily at low temperature and then shows a somewhat better balance between oxygen and carbon dioxide exchange than it does at normal temperature (Fig 17).

A more detailed comparison of the Teflon membrane lung and the human lung at basal conditions is revealing (Table IV). Oxygen and carbon dioxide gradients are approximately 15 times as great but this provides the proper carbon dioxide oxygen exchange ratio. The artificial blood film is 16 times thicker, and the transit distance more than 100 times greater, while the transit time is increased more than 200 times. Surprisingly, blood flows and gas exchange are about 10 times as much per square meter of membrane, but this is at the cost of a 40-fold increase in blood volume and more than a 25-fold increase in total volume. The size discrepancies are underlined by a look at the human lung microstructure as shown by electronmicroscopy (Fig 6).

The membrane lung described here has been used successfully to provide

gas exchange for clinical open-heart surgery (39-41), assisted circulation (41), and regional perfusion (38). The original clinical heart-lung machine employed either one or two separate membrane units operated in parallel to provide a total membrane area as large as 10 to 12 square meters of 0.5 mil Teflon (40). Patients up to 80 kilograms in weight were operated on satisfactorily by combining some degree of hypothermia with cardiopulmonary bypass. Lungs as small as two square meters have recently been used for open-heart surgery in infants, as small as 4.5 kilograms (10 pounds), at normal temperature with excellent gas exchange and control of blood volume. Another sandwich type lung using Teflon has been described by Esmond but clinical use has not been reported (30).

Case Report: Open-heart surgery at University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, June 2, 1960.

Case 1, an 11-year-old boy with easy fatigability and prominent dyspnea, was found to have a strong aortic murmur and thrill and a left ventricular-aortic gradient greater than 125 mm Hg. A routine valvuloplasty of a fused bicuspid aortic valve was carried out through a median sternotomy under moderate perfusion hypothermia. Weight was 28 kilograms, the membrane area eight square meters of 0.5 mil Teflon, and arterial flow 900 ml per minute (about 30 ml per kilogram per minute). Cooling was carried out on total bypass for 14 minutes to an esophageal temperature of 21°C. The aortotomy required 13 minutes and warming to 31°C esophageal temperature 18 minutes. During warming, flow was increased to 1400 ml per minute. Ventricular fibrillation was reverted with a single 60 cycle AC shock of 75 milliseconds and 135 volts at 25.6°C esophageal temperature. The total perfusion time was 47 minutes. Arterial and venous blood were well saturated and the pCO₂ remained at or below 40 mm Hg except briefly during the warming period. The lowest arterial pH was 7.25 and the eucapnic pH 7.35 (pH of arterial blood at 40 mm Hg pCO₂). The post operative course was uncomplicated and the patient showed marked clinical improvement.

This hypothermic procedure could probably have been carried out satisfactorily with a five square meter membrane lung of 0.5 mil Teflon. The membrane area provided (eight square meters) would have been satisfactory for perfusion at normal temperature. Had three mil Silastic on daeron been employed, about three square meters would have been sufficient (Fig 18). The use of the membrane lung facilitated lung volume control in the patient.

A portable assisted circulation unit incorporating a heat exchanger was constructed more than six years ago and used quite successfully in a few cases of which Case 2 is an example (41). A more sophisticated unit is now available consisting of a standard membrane lung, two Hufnagel pneumatic pumps,* and a heat exchanger (Fig 19). Either Teflon or silicone may be used as the diffusion membrane (Fig 18).

* Brunswick Manufacturing Company, Boston, Massachusetts.

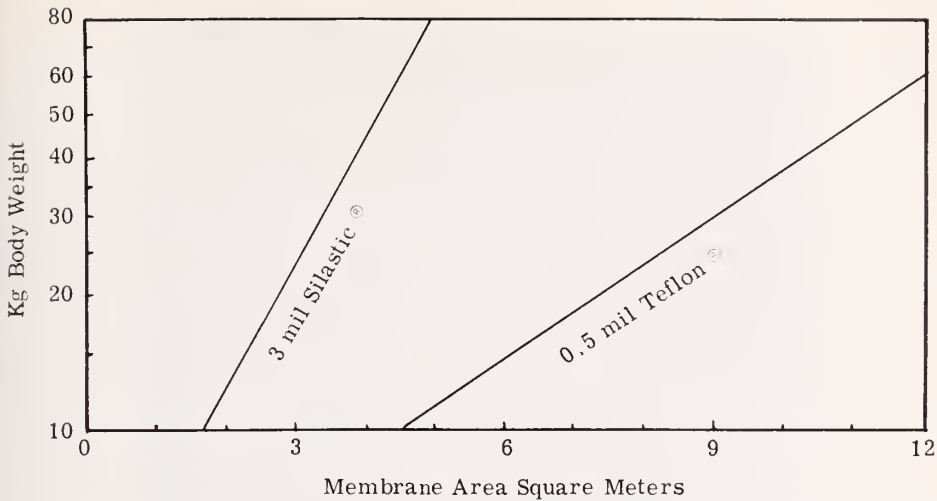


FIG. 18. The approximate membrane requirements for basal gas exchange are illustrated for 3 mil Silastic on dacron and for 0.5 mil Teflon. For Teflon, calculations are based on carbon dioxide exchange since this is less than oxygen transfer. A respiratory quotient of 0.8 is assumed. For 3 mil Silastic on dacron, oxygenation is the limiting factor and determines the necessary membrane area. (See Figure 22.)

Case Report: Assisted circulation to facilitate resection of "leaking" abdominal aortic aneurysm. Performed at East Tennessee Baptist Hospital, Knoxville, Tennessee, February 6, 1959.

Case 2, a 58-year-old white male with known arteriosclerotic heart disease and severe angina developed marked upper abdominal pain while hospitalized following a syncopal attack. A large, tender, pulsatile, upper abdominal mass was found on palpation. The tentative diagnosis of a wall dissection into an arteriosclerotic aneurysm was made and emergency arteriography was elected with resection to follow, should the diagnosis be confirmed. Since hypotension might easily precipitate severe myocardial ischemia, perfusion of the lower body during abdominal aortic occlusion to avoid post-occlusion hypotension was considered indicated. Arteriography under general anesthesia revealed a moderate sized aneurysm between the renal arteries and the aortic bifurcation. The patient was taken to surgery while still anesthetized and a routine resection and homograft replacement was carried out. Fresh hemorrhage into the aneurysmal wall was found. Inferior vena cava to femoral artery perfusion at a flow of approximately 500 ml per minute was carried out for somewhat more than 60 minutes during the aortic occlusion. Oxygenation was achieved with a five square meter 0.5 mil Teflon membrane lung. The circuit was arranged for constant volume control. The systolic pressure did not fall below 100 mm Hg on release of the aorta. Heparinization did not significantly complicate the surgery. The subsequent course was stormy because of chronic pulmonary disease and retained secretions but recovery was eventually quite satisfactory.

The equipment for this procedure was brought as an emergency from another

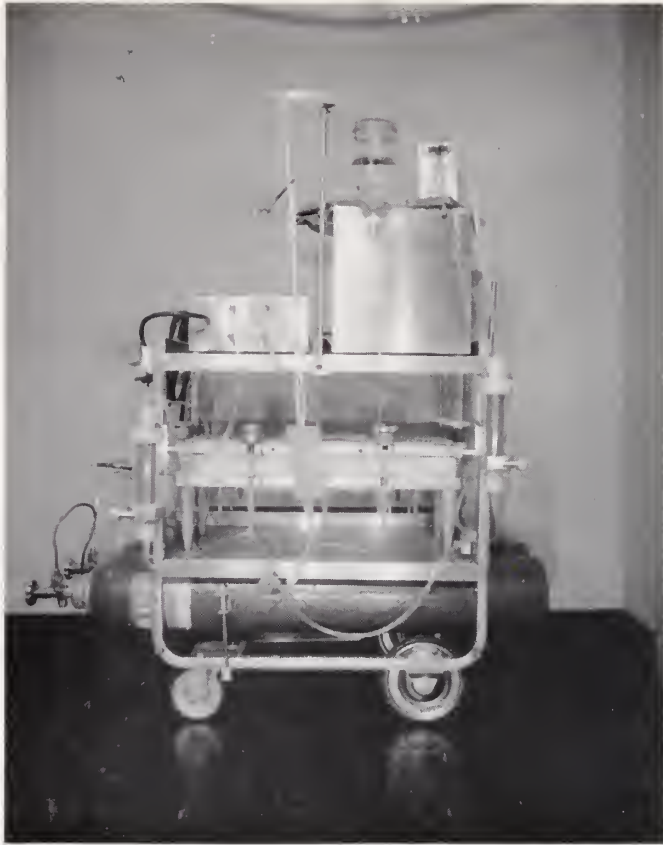


FIG. 19. A modern emergency membrane unit is shown. Two Hufnagel pumps are driven pneumatically. The perfusion circuit incorporates a lung, a small limited volume reservoir, a heat exchanger, and two bubble traps. It may be steam or gas autoclaved. The lung is pre-tested pneumatically before priming. The gas cylinders shown will drive the pumps for more than an hour and a line to attach the machine to wall oxygen or other pressure source is provided.

hospital and the perfusion was carried out with the help of a single technician. This was made possible by the low constant volume feature of the membrane lung which eliminates the need for close control. This type of apparatus is suitable for many varieties of assisted circulation and should be especially helpful where perfusions must be prolonged or where there is a personnel shortage.

A variety of regional perfusions, especially for neoplasms and osteomyelitis, have been carried out without difficulty (38). The membrane lung is again especially suited to this type of application because the blood volume may be fixed.

Case Report: Regional perfusion for osteomyelitis. Carried out at East Tennessee Tuberculosis Hospital, Knoxville, Tennessee, January 15, 1963.

Case 3, a 55-year-old white male was admitted October 15, 1962 with osteo-

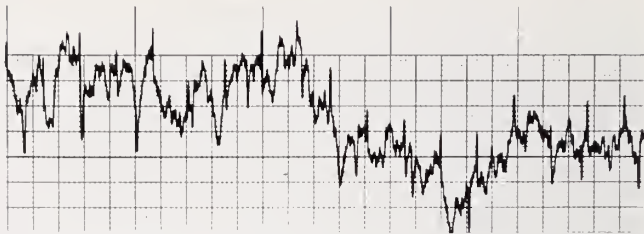
myelitis of the left femur and secondary infection of the soft tissue of the thigh. He was emaciated and weak. Examination showed a massive purulent infection involving the entire lateral and posterior left thigh. Much of the skin was necrotic and there were numerous draining fistulae. The knee had little free motion and there was considerable edema of the leg; no evidence of gross neurologic or circulatory deficiency was apparent, however. A radical debridement was carried out and revealed considerable muscle as well as skin and subcutaneous tissue involved in the necrotic process. Following an extended period of continuous irrigations, transfusion, massive antibiotic administration, and general supportive therapy, about two-thirds of the exposed muscle was successfully skin grafted. Drainage continued to be several ounces daily directly from the vicinity of the femur. It was felt that the condition of the patient would not permit anything but institutionalization unless drainage could be decreased and a regional antibiotic perfusion was elected. Cultured organisms included pneumococci, B streptococci, staphylococci aureus, and pseudomonas. Isolation perfusion was carried out via the distal femoral artery and vein with a tight rubber tube tourniquet held in place in the groin by a Steinman pin in the highest portion of the left iliac crest. A one square meter 0.5 mil Teflon membrane lung was employed in a normothermic perfusion circuit. The flow rate was approximately 100 to 200 ml per minute. During a perfusion of about 45 minutes, the blood volume of the patient was well maintained, a single transfusion of one unit being required. Penicillin 5,000,000 units, bacitracin 150,000 units, and Chloromycetin® 5 grams were administered into the perfusion circuit. There was temporary cyanosis of the extremity but no complications occurred. Subsequent drainage from the osteomyelitis was reduced to a few ml daily. Hospital discharge was possible on February 10, 1963 with the patient ambulatory. Slight drainage persisted to September 10, 1965 but the patient's general condition was good and he has continued ambulatory with the help of a cane, required only because of the stiffness of the knee.

Quite a small membrane lung is suitable for extremity perfusion since required blood flows are low (38). In this instance, cyanosis was probably secondary to vascular spasm resulting from the massive antibiotic administration rather than low blood flow since blood was well oxygenated and the arterial pH in the perfusion circuit remained within normal limits. The membrane lung is so simple to use for regional perfusion that it is probably the instrument of choice.

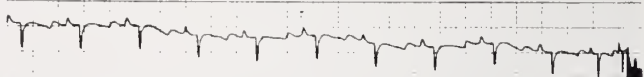
A small lung has been used for hypothermic perfusion of kidneys in storage by Humphries, Moretz, and Peiree (46). Successful reimplantation with simultaneous contralateral nephrectomy has been possible. The membrane lung has been used for perfusion of newborn lambs (47), the isolated perfusion of the pregnant sheep uterus (Fig 20) (48), the perfusion of isolated lactating mammary glands of goats (49), and for isolated liver perfusion (50). It has shown itself satisfactory for the treatment of experimental respiratory insufficiency (42). In addition, a tiny lung has been developed to provide equil-

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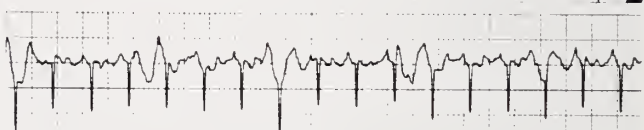
Control
From Abdomen
20 μ V/cm



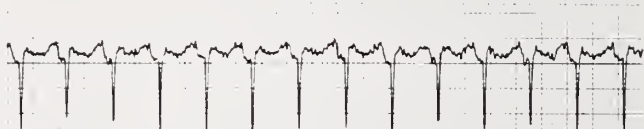
Maternal Lead I
1 mV/cm



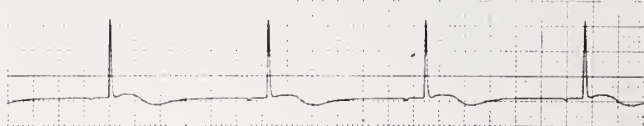
From Uterus
Isolated 33 min
40 μ V/cm
(119 min)*



From Uterus
Isolated 171 min
40 μ V/cm
(257 min)*



Direct Fetal
Not Perfused 10 min
0.5 mV/cm
(285 min)*



*** Total Perfusion Time.**

FIG. 20. Perfusion of the isolated pregnant sheep uterus has been satisfactory. Electrocardiograms obtained during such a perfusion are illustrated.

ibration of flowing blood with a fixed $p\text{CO}_2$ of 40 mm Hg (25). This device is being used in the development of a method of continuous acid-base measurement which uses two pH values (Fig 21). Others have reported the use of a variety of membrane devices for some of the above purposes and also as gills (51-54).

In addition to the pulmonary function of the membrane lung, it has been employed as a lung-kidney (placenta) (55), and for parabiotic or cross-dialysis (where one animal is dialyzed against another) (56). The device has been found to be particularly satisfactory as a kidney and has shown superior dialysance especially for creatinine, phosphate, and other larger molecules. It is successful as a relatively high flow pumpless kidney in both acute and chronic dialysis (57).

PROMISE

The ingenuity and success displayed in the design of new membrane lung devices attest to the need for them and their eventual successful recognition. Reference to Table III shows the theoretical gas exchange possible with Teflon and silicone. Figure 22 reveals that there is a progressive discrepancy be-

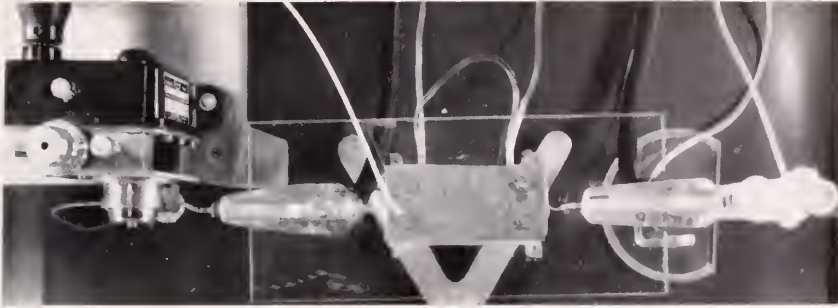


FIG. 21. Equipment for continuous double pH recording consists of the following, from left to right: tiny roller pump, glass electrode, membrane lung 10 cm in length with a blood volume of 0.1 ml, second glass electrode, and calomel cell. Arterial blood is pumped continually through the double electrode chamber. The membrane lung brings it to a fixed $p\text{CO}_2$ of 40 mm Hg.

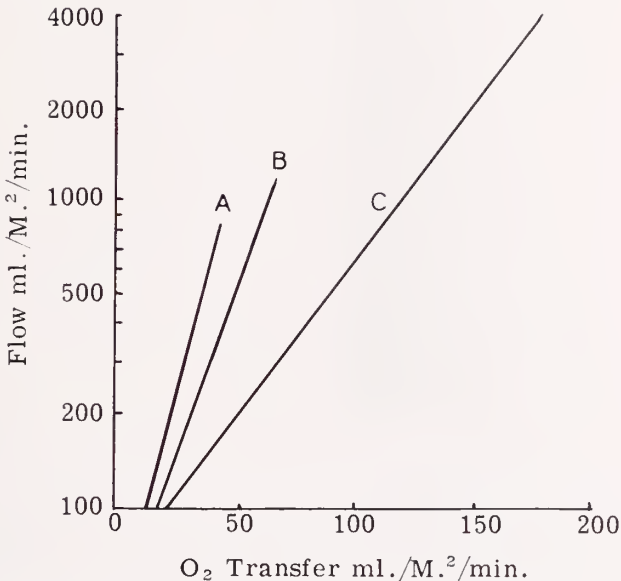


FIG. 22. Oxygen transfer in the membrane lung varies with blood flow:

- For 0.5 mil Teflon, oxygen transfer varies from approximately 15 to 40 ml per square meter per minute. Carbon dioxide transfer is limited to approximately 15 ml per square meter per minute.
- For 3 mil Silastic on dacron, oxygen transfer rises to approximately 65 ml per square meter per minute at 1100 ml per square meter per minute blood flow. Carbon dioxide transfer is the same order of magnitude.
- For 1 mil methyl silicone, oxygen transfer approaches 200 ml per square meter per minute at 4 liters per square meter per minute blood flow. Carbon dioxide transfer is satisfactory.

(Courtesy Trans Amer Soc Artif Intern Organs (25).)

tween theoretical exchange and what has actually been achieved in a membrane lung. Blood film geometry and agitation are the two major avenues available for improvement in gas exchange. Agitation, since it is simpler, has received the most attention.

Kylstra, Mouloupoulos, and Kolff (29) and Katsuhara, Kolff, and Taylor

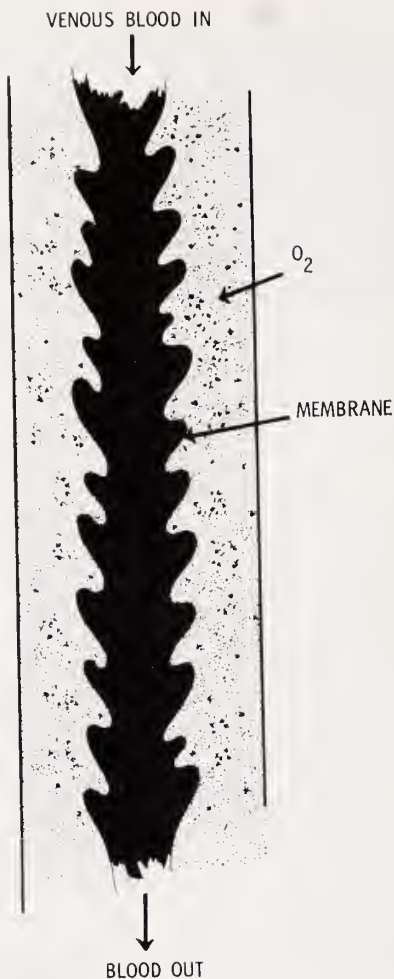


FIG. 23. The principle of agitation by cascading blood across an irregularly folded vertical membrane is illustrated. Kylstra, Mouloupoulos, and Kolff (29).

(58) have described a vertical, gravity fed lung using 1/8th mil Teflon. The Teflon is hung in folds to agitate the blood as it cascades over it (Fig 23). This lung has further been modified for the use of silicone membranes.

Crescenzi and Claff, following a variety of earlier efforts, have constructed a device utilizing fluctuating positive and negative air pressure to agitate films of blood between 1/4th mil Teflon membranes (59-61). Gas pulsations are produced 60 times a minute which results in alternating thick and thin blood films and considerable agitation (Fig 24). Neither the "Kylstra" nor the "Crescenzi" lung has the advantage of a fixed volume.

Thomas et al, in Paris, have described an unusual silicone membrane lung (62). The silicone membrane is made on a rotating drum by covering it with nylon mesh and dipping it in raw silicone "rubber" liquid. In use, the drum

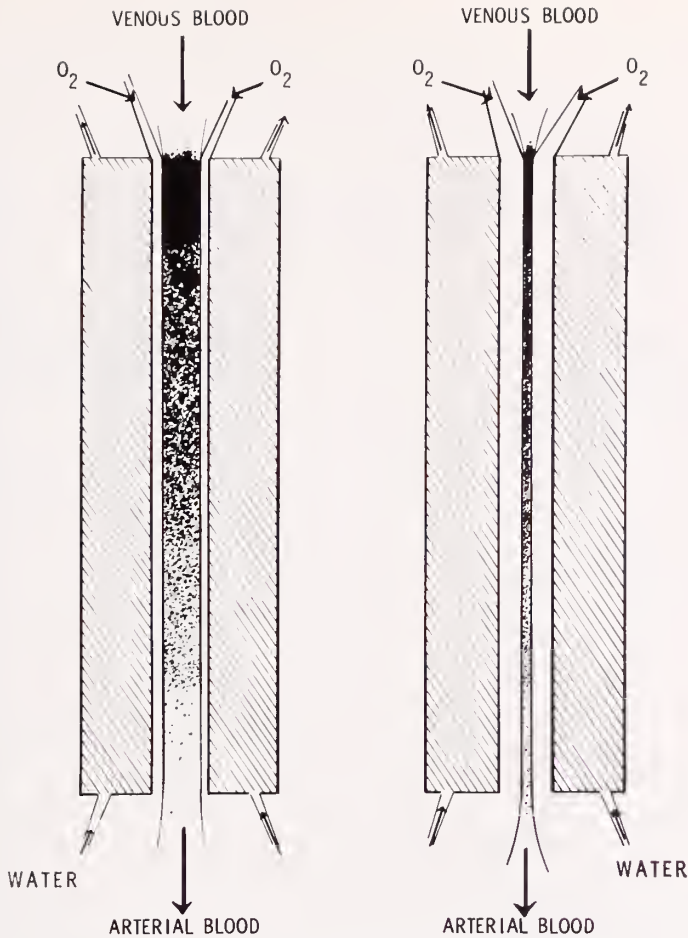


FIG. 24. Blood film agitation may be produced by applying rapidly alternating positive and negative pressure to the blood film by gas pulsation. This principle, with a 60 cycle per minute pulse, has been used by Crescenzi and Claff (61).

rotates with the blood on the outside of it, and an aerosol of oxygen and phosphate buffer is sprayed on the inside. Gas exchange is through the silicone "rubber." The rotation of the drum would be expected to produce a considerable degree of agitation of the blood film (Fig 25). Clinical work with this machine has been carried out since 1956 but, unfortunately, there have been no recent reports.

Bodell et al have passed oxygen under pressure through tiny silicone rubber tubes over which blood flows (Fig 26) (63, 70). The small units contain ten 10 to 15 foot lengths of silicone tubing with a 6.5 mil wall. Twenty of the small units are coupled together, the blood flowing through them by gravity. As many as four large units have been used in a bank to give a total membrane area up to 4.5 square meters. Pumping blood through the machine with a strong pulse produces agitation and improves oxygen transfer. A somewhat

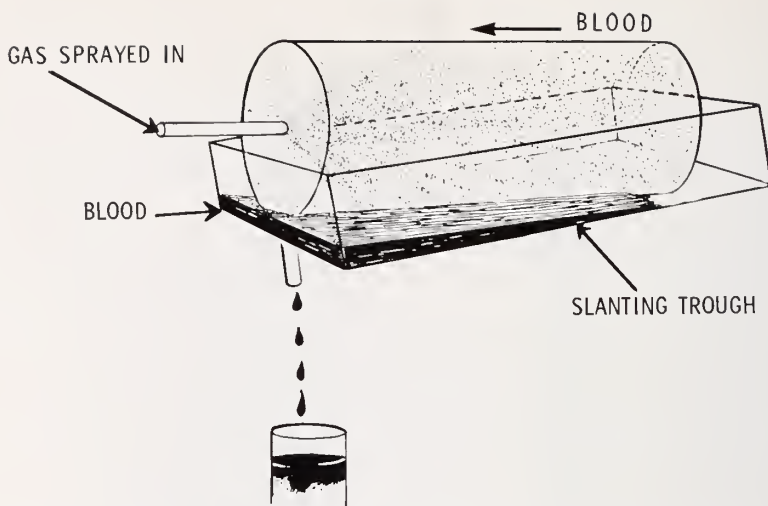


FIG. 25. Silicone membrane of Thomas et al (62). Blood on the outside of a rotating silicone drum is oxygenated from an aerosol of oxygen and buffer sprayed into inside of cylinder. Agitation is produced by rotation of cylinder.

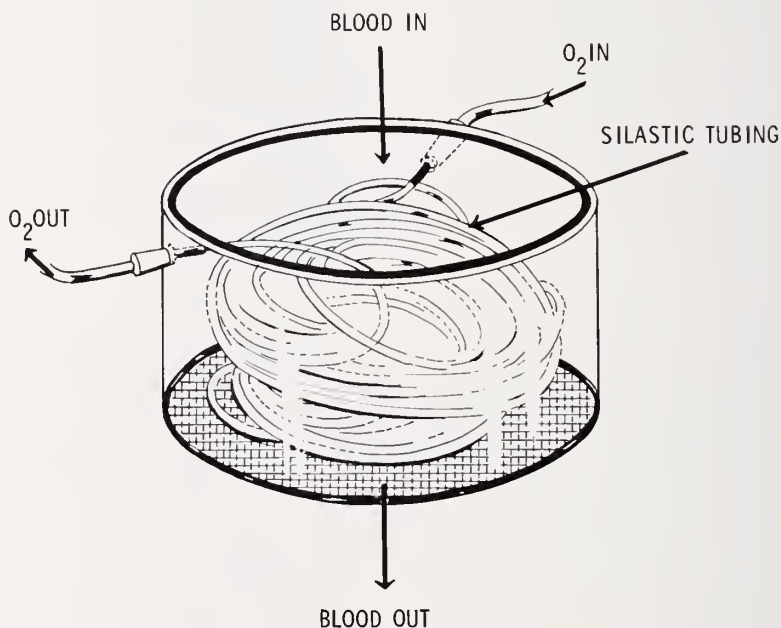


FIG. 26. The device of Bodell et al which exchanges oxygen passing through multiple small silicone tubes, while blood passes across the tubes in a pulsatile fashion, is shown diagrammatically (63).

similar device has been described by Wilson, Shepley, and Llewellyn-Thomas (54).

Day et al and Crystal et al have reported a silicone membrane lung consisting of a number of wide, long, reinforced silicone envelopes (65-66).

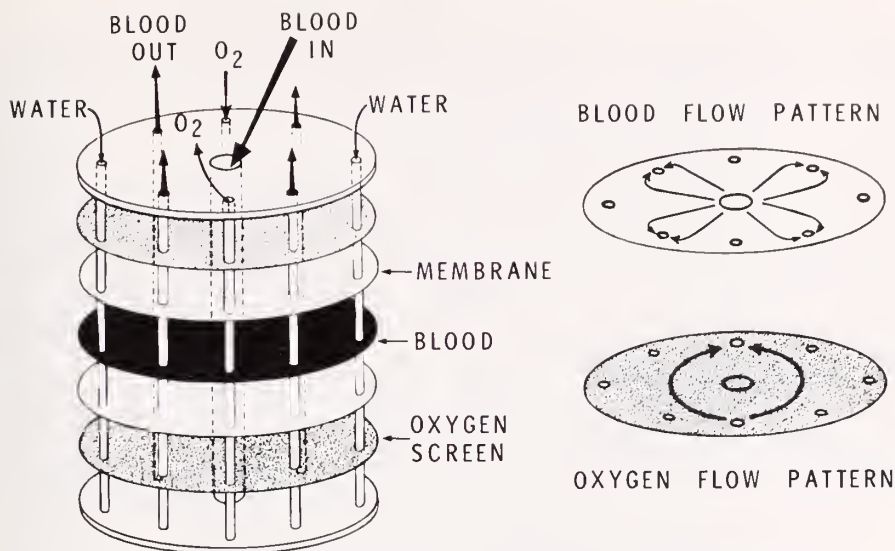


FIG. 27. The basic functional unit and the approximate distribution pattern for blood and gas is shown for the silicone membrane lung of Bramson et al (68). Agitation is produced by a polyvinyl coated fiber glass screen inserted between the membranes.

Blood flows between the membranes by gravity, and agitation is secured by tilting them back and forth at a 45 to 60 degree angle.

Kolabow and Bowman have utilized prefabricated heart-lungs with a flat tube of reinforced silicone containing a screen stent (67). This is wrapped about a central core, and oxygen under negative pressure is passed through it. Blood flows across the loops of flat tubing containing the oxygen.

Marks, Baldwin, and Miller have reported a fixed volume high prime lung where agitation is produced by a Mylar® screen insert between relatively thick (5 mil) reinforced silicone sheets that have been glued together to form closed bags (31). Exchange is quite good since the screen insert produces a considerable degree of agitation. More recently, Bramson et al have elaborated the same principle in an apparently practical clinical lung by incorporating two 10 mil fiber glass screens between silicone membranes (68). The blood film dimensions are maintained within the desired limits by hydraulic pressure. The water also provides for satisfactory heat exchange (Fig 27). Similar fiber glass screen separators employed with silicone membranes in the lung herein reported have provided oxygenation as high as 65 ml per square meter per minute but only at the expense of rather large blood volumes (Fig 28) (25). The use of a screen separator between membranes can doubtless be refined greatly. Use of a thinner fiber in the direction of blood flow, for instance, permits blood volume reduction while retaining some degree of agitation. The published performances of a variety of membrane lungs are compared in Table V. Reports by Esmond (69), Thomas et al (62), and some others lack sufficient data for comparison and so are omitted.

The geometry of the blood film can be greatly improved by incorporating



FIG. 28. A silicone membrane envelope incorporating a polyvinyl coated fiber glass screen of the type used by Bramson et al (68). These may be fabricated and pre-tested. Eight are required for one square meter of membrane. The membrane area needed is shown in Figure 18.

TABLE V
Comparison of Some Membrane Lungs

	Membrane & size mils	Volume ml/M ²	Agitation	Unit Size M ²	O ₂ /M ² /min	Flow ml/ M ² /min
Clowes (7)	Teflon 1/2	130 F	No	0.5	22	?
Peirce (25)	Teflon 1/2	140 F	No	0.125	30	500
Crescenzi (61)	Teflon 1/4	? V	± Gas Pulse	0.46	?	800
Kylstra (29)	Teflon 1/8	180 V	Cascades	0.365	69	700
Bramson (68)	Silicon 10-15 S	180 F	Insert	5.6	35 ?	1000
Marx (31)	Silicone 5 S	340 F	Insert	0.32	63	1800
Peirce (71)	Silicone 3 S	250 F	Insert	0.125	65	2000
Bodell (70)	Silicone 6.5	250 F	Blood Pulse	0.096	83	500
Day (66)	Silicone 2 S	250 V	Rocking	0.63	100 ?	1000
Kolobow (67)	Silicone 4 S	90 F	- Gas Pulse	1.2†	100	1100

* Available commercially or semi-commercially.

† Entire machine including pump.

S, Supported synthetic cloth; F, Fixed volume (relatively); V, Variable volume.

Volumes and gas exchange are only approximately correct. They correspond to the flow listed which is also generally the maximum useful flow. Several devices, for which available data are grossly incomplete, have been omitted.

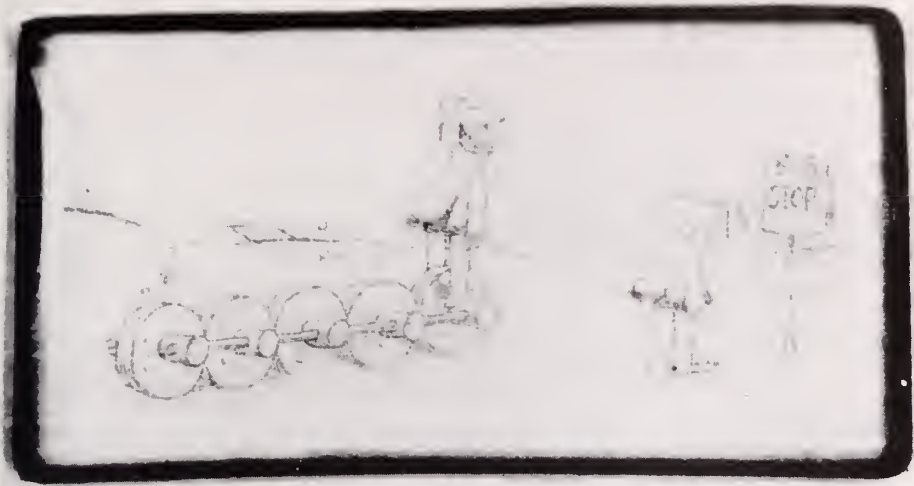


FIG. 29. The stickiness of a 1 mil thick methyl silicone membrane mounted on a wire frame is demonstrated effectively by a simple "rubbing" from the comic strip "B. C.". This stickiness makes it difficult to utilize two silicone membranes together without some sort of separator between them.

a blood flow pattern on a thinner and less crude membrane (25). For silicone membranes, simple refinement of the external support is not satisfactory because the membranes tend to stick together and prevent full filming of the blood. Using one mil silicone, Esmond and Dibelius were successful in oxygenating only 115 ml of venous blood per minute using a 900 square centimeter unit (30). This would indicate a transfer of less than 100 ml of oxygen per square meter per minute. The extreme stickiness of most silicones, well illustrated by the ability of "silly putty" to pick up the picture from a freshly printed page, can be demonstrated by taking a simple "rubbing" from a newspaper (Fig 29). Insertion of a separator between the membranes produces too crude a blood film for one mil silicone but a multiple point pattern can be transferred to a somewhat thicker silicone membrane that is then used in conjunction with the thin silicone (25). An intrinsic support membrane has been made by using a halftone screen as an engraving plate and a medical grade room temperature curing silicone to fill the depressions in the halftone screen.* Employing a small instrumental lung and an area of one mil silicone of approximately 11 square centimeters, it has been possible to secure blood flows of four liters per square meter per minute, oxygen transfer of 196 ml per square meter per minute, and carbon dioxide transfer as high as 238 ml per square meter per minute. The blood film formed is approximately 100 microns thick but nearly all of the gas transfer occurs on one side through the one mil membrane. It is hoped that a more precise cone point pattern can be transferred to one mil silicone membrane. This would almost double the membrane area available for gas exchange.

* Hardy Products Company, Decatur, Georgia.

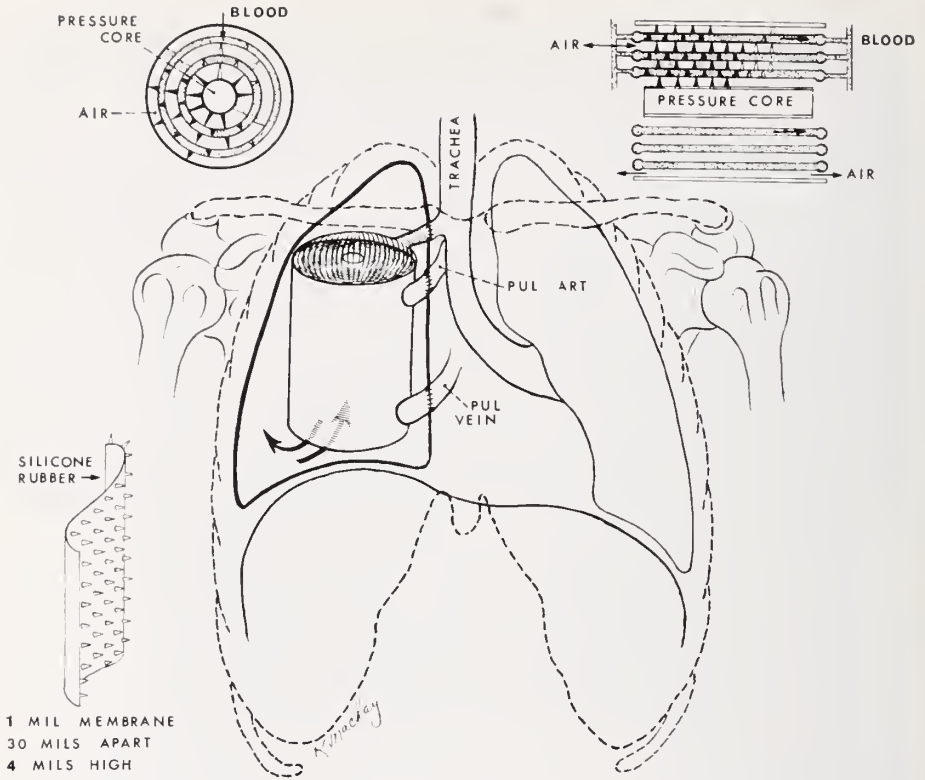


FIG. 30. This is a sketch to show a concept for an implantable membrane lung utilizing ultra-thin silicone membrane with intrinsic point support. Details of possible air and blood manifolding are shown. Except for the pressure core, the case, and the manifold, the entire apparatus would have functional gas exchange thereby greatly reducing the necessary size. See text.

(Courtesy Trans Amer Soc Artif Intern Organs (25).)

A delicate self supporting membrane could well be utilized as the starting point in the construction of an implantable lung. Such a lung could be quite small because the intrinsic support pattern would form numerous active capillaries and very little material aside from actual functioning membrane would be required. Such an implantable lung might best occupy the pleural space, receive its gas as air from the trachea as a result of normal respiratory movement, and be perfused by blood driven through it by the normal pressure of the pulmonary artery (Fig 30). The plural space could be effectively exteriorized by lining it with silicone membrane backed by a material into which tissue could grow. Installation of the pleural lining could be done as a preliminary stage together with pneumonectomy and formation of a small pulmonary artery to pulmonary vein fistula. The lung could then be inserted by only three anastomoses, without the use of cardiopulmonary bypass. Such a lung would have only a central core and a shell that were not actually functioning elements. If one mil silicone membrane were used, one to two

square meters might provide as much as 200 ml of oxygen and carbon dioxide exchange per minute, using air as the respiratory gas. Of course, the formidable biologic problems, especially those of clotting within the artificial lung, may prevent the construction of such an implantable unit for a long time. The possibility of implanting a lung, however, has been shown by Bodell who utilized a long Teflon graft containing ten, 10 foot silicone tubes to which oxygen was supplied under pressure (64). The graft went from the pulmonary artery to the left atrium, and he was able to demonstrate a rise in oxygen tension and fall in carbon dioxide tension in aortic blood when blood and gas were flowing. Although the maximum possible function of this implantable unit would be about eight ml of oxygen exchange per minute, these experiments are very important in demonstrating the potential feasibility of implanting an artificial lung.

SUMMARY

Despite the current clinical disregard for the membrane lung, its clear cut superiority in gentle blood handling and its ease of circuit control indicate that it is a worthwhile device justifying considerable developmental effort. At the present time, several commercial devices are available and a number of workers are actively experimenting with improvements and new designs. The membrane lung has been used with considerable success clinically for open-heart surgery, assisted circulation, and regional perfusion. It is quite practical for applications not requiring flows over 2000 to 2500 ml per minute but may, in several forms, be used for full flow support. For gas exchange in the perfusion of small subjects it has no equal because of its adjustable capacity and the ease of close blood volume control. Teflon membrane and silicone membrane are now both available, the former being relatively inexpensive but of limited gas exchange, and the latter, though expensive, being potentially far superior as an exchange membrane. It would appear that more widespread clinical use of the membrane lung is indicated despite its relatively early stage of evolution.

The improvement of gas transfer by utilizing ultra-thin silicone membranes and an intrinsic membrane support pattern forming microcapillaries is reported. A theoretical approach to an implantable lung is also presented.

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Myasthenia Gravis and Thyroid Disease: Clinical and Immunologic Correlation

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INTRODUCTION

Interest in clinical relationship between myasthenia gravis and thyroid disease has been evident since the turn of the century (1). Recently, some attention has been given to immunologic relationships between these two diseases and their possible significance. Antibodies to thyroid substrate have been found in a substantial number of sera from myasthenic patients although the significance of these antibodies and whether they are an expression of concomitant thyroid disease in the myasthenic are not evaluated in these reports. Correlations between findings of antibodies to striated muscle and thymus epithelial cells as visualized by immunofluorescence technique and clinical state of the myasthenic patient have been reported by Weiner and Osserman (2).

Whether relationship between myasthenia gravis and thyroid disease is coincidental or whether the two diseases are significantly related has only been correlated by clinical evaluation. Sahey et al (3) suggested that this relationship is a chance one and that more careful investigation along other lines is needed.

In view of coincidental clinical association between myasthenia gravis and thyroid disease, primarily hyperthyroidism (4-9), and recent reports of a relatively high incidence of finding thyroid antibodies in sera from myasthenic patients (10-15), a more definitive study was undertaken in order to: (a) determine if clinical association between myasthenia gravis and thyroid disease is significant in a larger sample; (b) determine if such clinical association can be substantiated by immunologic testing for antithyroid antibodies; (c) correlate these antibody findings with the patients' thyroid and myasthenic status to determine if the antibodies in sera from myasthenic patients are an expression of concomitant thyroid disease or the result of a different mechanism; and (d) determine if there is any relationship between antithyroid antibodies found and antibodies to striated muscle and thymic epithelial cells in sera from myasthenia patients.

MATERIAL

I. Sera

Myasthenic. Two hundred sterile sera were chosen consecutively from a total of over 1000 collected from 350 patients attending the Myasthenia Gravis Clinic

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of The Mount Sinai Hospital, New York. In each instance an unequivocal diagnosis of myasthenia gravis had been established by history, physical examination, response to edrophonium (Tensilon) chloride, neostigmine (Prostigmin) as compared to placebo. In some instances electromyography with or without d'tubocurarine was used as a confirmatory test. All pertinent data on each patient were recorded. Serum samples used labeled with a code number, had been stored at $+4^{\circ}\text{C}$ for a period of 1 to 2 years. All readings were made by at least two investigators independently. Codes were not broken until completion of experiment. Sera used in this study were from:

1. 114 patients with myasthenia gravis without other recognized systemic disease
2. 39 patients with myasthenia gravis and thyroid disease
3. 16 patients with myasthenia gravis and systemic lupus erythematosus or rheumatoid arthritis
4. 31 patients with myasthenia gravis and other diseases (e.g., diabetes mellitus, cancer, gout, asthma, peptic ulcer).

All coded sera were compared with known positive and negative sera in each series of tests.

Controls. One hundred fifty individuals provided sera for study:

1. 52 individuals with no documented disease
2. 13 patients with either lupus erythematosus or rheumatoid arthritis
3. 10 patients with various myopathies
4. 12 patients with diabetes mellitus, cancer, asthma, peptic ulcer
5. 63 patients with various thyroid disease states of which 22 had Hashimoto's disease (20 with histologic confirmation).

II. Antigens

Thyroid. Monkey thyroid tissue and thyroid tissue taken from thyrotoxic patients at surgery were used as substrates for immunofluorescent studies. There was no appreciable difference in immunofluorescent reactions between the two kinds of tissue. All tissues were quick-frozen in a mixture of dry ice and methanol at -70°C and kept at -20°C in a cryostat.

Muscle and Thymus. Striated muscle tissue from rats and calf thymus frozen by the above method were used as substrates in detection of antimuscle (A-Bands) antibodies and antibodies to thymic epithelial cells respectively.

Tanned-Sheep-Red-Cells. Purified human thyroglobulin prepared by method of Derrien et al (16) was used in coating red cells according to modified method of Roitt and Doniach (17).

Agar Gel Medium. Medium was used in 122 sera for detection of antibodies by the precipitin test.

METHOD

I. Detection of Thyroid Antibodies

Immunofluorescence. Sections of frozen thyroid tissue were cut in cryostat 6 microns thick and air dried at room temperature for 15 to 30 minutes. Tissue

was then fixed in acetone for 10 minutes and washed with phosphate-buffered-saline (PBS), pH 7.5, 0.01 M. Test sera diluted to 1:10 with PBS were applied for 30 minutes. After excess serum was thoroughly washed off with PBS, fluorescein-conjugated rabbit antihuman γ -S gamma globulin 1:50 was applied for 30 minutes. After a third washing (30 minutes) with PBS, sections were mounted in Elvanol and examined by fluorescence microscopy using an ultraviolet-passing BG-12 filter with a peak at 405 millimicrons and a blue-green ultraviolet light excluding filter placed in eyepiece of microscope.

Hemagglutination (tanned-red-cell agglutination test). Aliquots of sera were heated at constant 56°C temperature for 30 minutes to remove complement. Test sera diluted 1:5 were further diluted with sterile isotonic saline to give concentrations from 1:25 through 1:2,500,000. After addition of 0.1 cc of thyroglobulin-coated red-cells to 0.1 cc of test serum dilution and to a control, all test material was shaken in sterile tubes (all glassware was first washed then permitted to stand in $\text{H}_2\text{SO}_4\text{-K}_2\text{Cr}_2\text{O}_7$ solution for approximately 24 hours, then rinsed thoroughly to avoid contamination in test) and kept at 4°C overnight for reading next day. This test is considered by many the most sensitive method available for detection of thyroglobulin antibodies. In autoimmune thyroiditis, titers of 1:25,000 and upwards to several million have been reported (18). Low titers (1:5–1:250) have been reported in a substantial number of autoimmune thyroiditis patients but are considered nonspecific in many diseases studied immunologically.

Precipitin Test. A 0.5% solution of Nobel agar was prepared in PBS, pH 7.2 and poured into standard Ouchterlony plates. Antigen consisted of thyroglobulin prepared by the method of Derrien, Michell and Roche (16) which was placed in the center well. Undiluted test sera were placed in the peripheral wells. Plates were kept in the refrigerator at 4°C and were read at 24 hour intervals for three days for appearance of precipitin lines. Studied were sera of 75 myasthenics with and without concomitant thyroid disease, 22 sera of patients with Hashimoto's disease and sera of 25 normal controls. This test, although considered less sensitive than the tanned-red-cell hemagglutination test, is more specific for detection of thyroglobulin antibodies in patients with Hashimoto's disease.

II. Detection of Antimusele and Antithymic Epithelial Cell Antibodies

Immunofluorescence. Immunofluorescent studies were performed on all sera by the method described for thyroid antibodies except that rat muscle and calf thymus were used as substrates. These sera were diluted 1:60 to rule out false positive reactions based on our experience and that of other investigators (19).

III. Clinical Evaluation of Patients

Thyroid Status. Records of 801 myasthenia gravis patients were carefully studied for evidence of thyroid dysfunction or disease. Measurements of protein-bound iodine (PBI), radioactive iodine uptake (I^{131}), triiodothyronine suppression test (T_3), and even basal metabolic rates (BMR) in very early records were noted. At the time of physical examination size and consistency of the

thyroid gland were recorded. Histologic evidence either from surgical pathologic specimens or autopsy reports of thyroid gland was noted. All but 94 patients were evaluated for thyroid status by these methods. Most of these 94 patients were cases seen in our earlier experience before modern thyroid testing was available and are either dead or lost to follow-up. Of 350 human sera (myasthenics and controls) studied immunologically, only 4 myasthenics had no thyroid evaluation. Patients' thyroid status was redetermined at time of blood drawing.

Myasthenic Status. All myasthenic patients were evaluated according to Clinical Classification of Myasthenia Gravis by Osserman (1) as follows:

Group I—Ocular. Involvement of single muscle group, mostly ocular, appearing as ptosis and diplopia. Very mild; no mortality.

Group II A—Mild Generalized Myasthenia Gravis. Gradual onset, frequently presents with ocular symptoms spreading to generalized involvement of skeletal and bulbar musculature. Respiratory system not involved. Usually mild; very low mortality.

Group II B—Moderate Generalized Myasthenia Gravis. Gradual onset, group includes ocular involvement with moderately severe skeletal and bulbar involvement. Respiratory system not involved. Low mortality.

Group III—Acute Fulminating. Rapid onset of severe bulbar and skeletal muscle weakness with early involvement of respiration. Very severe; high mortality.

Group IV—Late Severe. Exacerbation of Group I or II patient approximately 2 years after onset of disease. Symptoms and course similar to Group III.

Severity of myasthenia gravis was ascertained at time of blood drawing. Pre- and post-thymectomy patients are included in study.

RESULTS

Table I presents thyroid status of 801 myasthenics screened for thyroid dysfunction. One hundred five patients (13.1%) were found to have some type of thyroid disorder: 42 (5.3%) had hyperthyroidism, 46 (5.7%) had hypothyroidism and 17 (2.1%) had nontoxic goitre (2 patients had Hashimoto's

TABLE I
Classification of Thyroid Status

Thyroid status	No. of patients	Percentage
Euthyroid	602	75.2
Hyperthyroid*	42	(5.3)
Hypothyroid	46	(5.7)
Nontoxic goitre*	17	(2.1)
Not evaluated	94	11.7
	801	100

* One Hashimoto's disease in each group.

TABLE II
*Comparison of Immunofluorescence and Hemagglutination Reactions
 for Thyroid Antibodies in 350 Human Sera*

Clinical status	No. of patients	Imunofluorescent antibodies			Hemagglutination antibodies			Both	
		Pos	Neg*	% Pos	Pos	Neg*	% Pos	Pos	% Pos
M.G.† with thyroid disease	39	16	23	41	18	21	46.2	15	38.4
Thyroid disease controls	63	33	30	52.4	32	31	50.8	20	31.6
M.G.† with other diseases	47	7	40	15	13	34	27.5	5	10.6
Other disease controls	35	3	32	9.4	6	29	20.7	2	5.7
M.G.† only	114	19	95	16.7	28	86	24.6	15	13.2
Normal controls	52	2	50	3.8	1	51	1.9	1	1.9
Total	350								

* Includes \pm and + immunofluorescence reactions and 1:5 hemagglutination titers.

† Myasthenia gravis.

disease confirmed by histologic findings). Ninety-four patients were not evaluated.

Two hundred sera from these 801 myasthenic patients plus 150 controls were studied by immunofluorescence and hemagglutination techniques. Sixty-five sera selected at random from myasthenics with antithyroid antibodies and 10 without such antibodies were studied by precipitin test (clinical evaluations were correlated after immunologic studies were completed).

Table II is a comparison of immunofluorescent and hemagglutination reactions for antithyroid antibodies in these 350 sera. Results are recorded as positive and negative (includes plus minus, plus minus to one plus immunofluorescent reactions and 1:5 hemagglutination titers). Of interest is the finding of antithyroid antibodies in patients with myasthenia gravis only. In 114 patients 16.7% showed positive immunofluorescence findings and 24.6% had significant hemagglutination titers compared with only 3.8% and 1.9% positivity respectively in 52 normal controls. Differences in percentages based on a median test is significant at level of p less than 0.05 for immunofluorescence and p less than 0.001 for hemagglutination titers. Forty-seven sera from myasthenic patients without thyroid disease but with other diseases were compared with sera from 35 patients without myasthenia gravis or thyroid disease but with comparable other diseases. The p value between these two groups and patients with myasthenia gravis only is not significant. If the sera of patients with lupus erythematosus and rheumatoid arthritis are excluded from the 35 other disease controls there is a significant p value at level of less than 0.04 between these controls and myasthenia gravis only in the hemagglutination test. No significance is found with the immunofluorescence test as p value is less than 0.022. Thyroid hemagglutination antibodies when compared to normal population and other diseases not producing antibodies are greater than

TABLE III
*Comparison of Thyroid Antibodies in Myasthenia with Thyroid Disease
 and Controls with Thyroid Disease*

Clinical status	No. of patients	Immunofluorescent antibodies		Hemagglutination antibodies		Both
		Pos	Neg	Pos	Neg	Pos
<i>M.G.* with Thyroid Disease:</i>						
Hyperthyroidism	19	8	11	10	9	8
Hypothyroidism	13	6	7	6	7	5
Nontoxic goitre	5	0	5	0	5	0
Subtotal	37	14 (38%)	23	16 (43%)	21	13 (35%)
Hashimoto's disease	2	2	0	2	0	2
TOTAL	39	16 (41%)	23	18 (46%)	21	15 (38%)
<i>Thyroid Controls:</i>						
Hyperthyroidism	23	10	13	9	14	3
Hypothyroidism	13	7	6	7	6	5
Nontoxic goitre	5	1	4	0	5	0
Subtotal	41	18 (44%)	23	16 (39%)	25	8 (20%)
Hashimoto's disease	22	15	7	16	6	12
TOTAL	63	33 (52%)	30	32 (51%)	31	20 (32%)

* Myasthenia gravis.

would be expected by chance alone. However, there is no significant difference in p values between sera of non-autoimmune disease controls and myasthenia gravis with similar secondary diseases.

Of 39 patients with myasthenia gravis and thyroid disease, sera of 41% had positive immunofluorescence and 46% had significant hemagglutination titers between 1:25 and 1:2,500,000 as compared to 52% and 51% respectively in sera of controls with similar thyroid disease without myasthenia. There is no significant p value between these percentages based on chi square test.

Relationship between immunofluorescent antibodies to muscle, thymus and thyroid tissue and evaluation of thyroid status in 196 myasthenic patients and controls is illustrated in Table IV. Antibody results of 4 sera are not included in this Table because thyroid status could not be determined. One of these 4 sera demonstrated strongly positive thyroid immunofluorescence finding and a hemagglutination titer of 1:2500. This patient had diabetes mellitus. The other three sera had no thyroid antibodies. Four sera of 19 hyperthyroid patients and 1 of 13 sera from hypothyroid myasthenic patients demonstrated antibodies to all three substrates, whereas 20 sera of 157 (12.7%) from euthyroid myasthenic patients showed these three antibodies by immunofluorescence. Four of these 20 euthyroid sera were from patients who had myasthenia gravis and other concomitant diseases such as cancer, gout, diabetes mellitus, rheumatoid

TABLE IV
*Relationship between Immunofluorescent Antibodies and Thyroid Status
 of Myasthenic Patients and Controls*

Thyroid status	Sex	Muscle and thymus positive		Muscle and thymus negative		% Positive Muscle, thymus, thyroid antibodies
		Thyroid positive	Thyroid negative	Thyroid positive	Thyroid negative	
Euthyroid	F	15	25	2	58	20/157
157 (excluding 4 non-eval.)	M	5	26	3	23	12.7%
Hyperthyroid	F	2	3	4	5	4/19
19	M	2	1	0	2	21%
Hypothyroid	F	1	1	4	4	1/13
13	M	0	1	1	1	7.7%
Goitre	F	0	2	1	0	0/5
5	M	0	0	0	2	0%
Hashimoto's disease	F	1	0	1	0	1/2
2						50%
TOTAL		26	59	16	95	26/196
196						13.8%
<i>Controls</i>						
Normals	52	0	0	2	50	0
Thyroid disease	63	0	0	33	30	0
Other diseases	35	0	0	3	32	0
TOTAL	150	0	0	38	112	0

arthritis, lupus erythematosus, etc. Five other sera from euthyroid patients demonstrated thyroid antibodies only; one serum was from a myasthenic without any concomitant disease. None of the sera from normal or other disease controls demonstrated muscle or thymus antibodies. This Table indicates that a small percentage of sera from myasthenics without concomitant thyroid dysfunction have multiple antibody production, since muscle and thymic antibodies were also present.

Precipitin tests were performed on 65 sera from myasthenic patients (including all associated with clinical thyroid dysfunction) with demonstrable hemagglutination and/or immunofluorescent antithyroid antibodies and on ten sera from myasthenics without thyroid antibodies. Three of 65 sera had significant positive precipitin reactions. These were from patients with concomitant thyroid disease with positive hemagglutination and immunofluorescent antibodies (one Hashimoto's disease, one hyperthyroid, one nontoxic goitre). The other sera from a myasthenic with Hashimoto's disease (hemagglutination titer

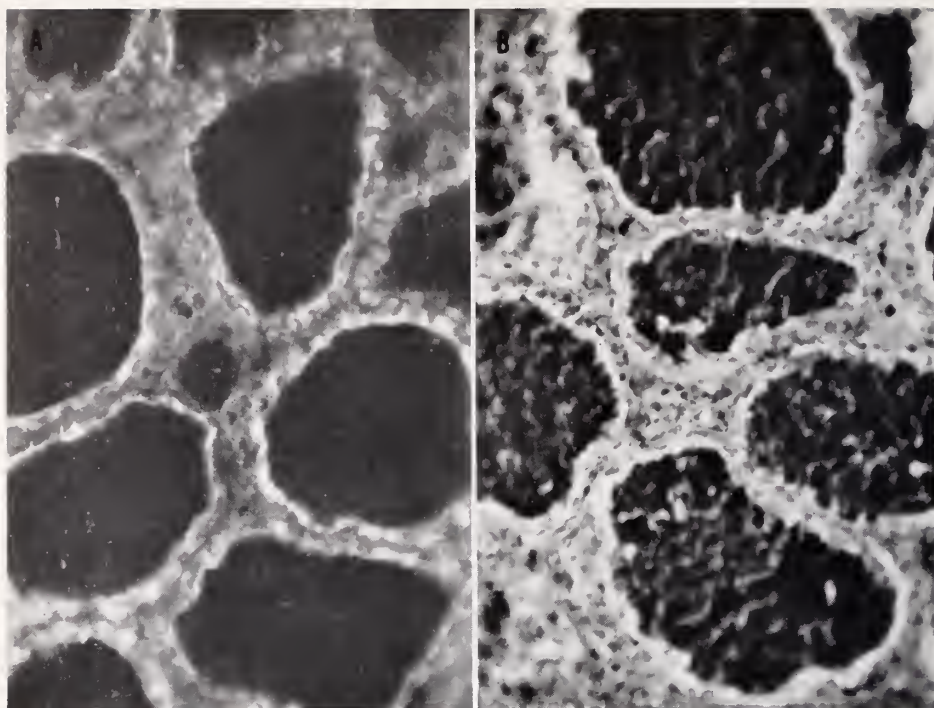


Fig. 1. Immunofluorescent Staining of Thyroid Tissue. A. Negative reaction showing no immunofluorescence of either epithelial cells or colloid; B. Positive reaction. Indirect methodology with serum diluted 1:10.

1:250) displayed no antibody in the precipitin test. Ten sera from myasthenics without thyroid antibodies and 25 of 52 normal sera tested did not demonstrate antibodies in the precipitin test. Sixteen of 22 patients' sera who had Hashimoto's disease had significant antibodies in precipitin testing.

CASE REPORTS: MYASTHENIA GRAVIS WITH HASHIMOTO'S DISEASE

1. Female, age 43, Group II B myasthenic whose myasthenia gravis preceded development of nontoxic goitre by six years. A sub-total thyroidectomy was performed. Histologic examination showed typical changes of Hashimoto's disease. Pre- and post-thyroidectomy sera were strongly positive for immunofluorescent antithyroid antibodies (muscle and thymus negative) and showed a hemagglutination titer of 1:5-1:2,500,000. Precipitin test was strongly positive.

2. Female, age 20, Group IV myasthenic whose symptoms began 14 months prior to appearance of toxic nodular goitre. Two years after a sub-total thyroidectomy and just prior to thymectomy, serum revealed positive immunofluorescent antibodies to thyroid epithelial cells only, hemagglutination titer of 1:5-1:250 and a negative precipitin test. Antibody findings to muscle and thymus were present. No pre-thyroidectomy sera were obtained. Microscopic examination of thyroid tissue revealed a diffuse chronic thyroiditis typical of Hashimoto's disease.

Table V shows hemagglutination titers in sera of myasthenic patients with and without thyroid disease and the number of positive immunofluorescent

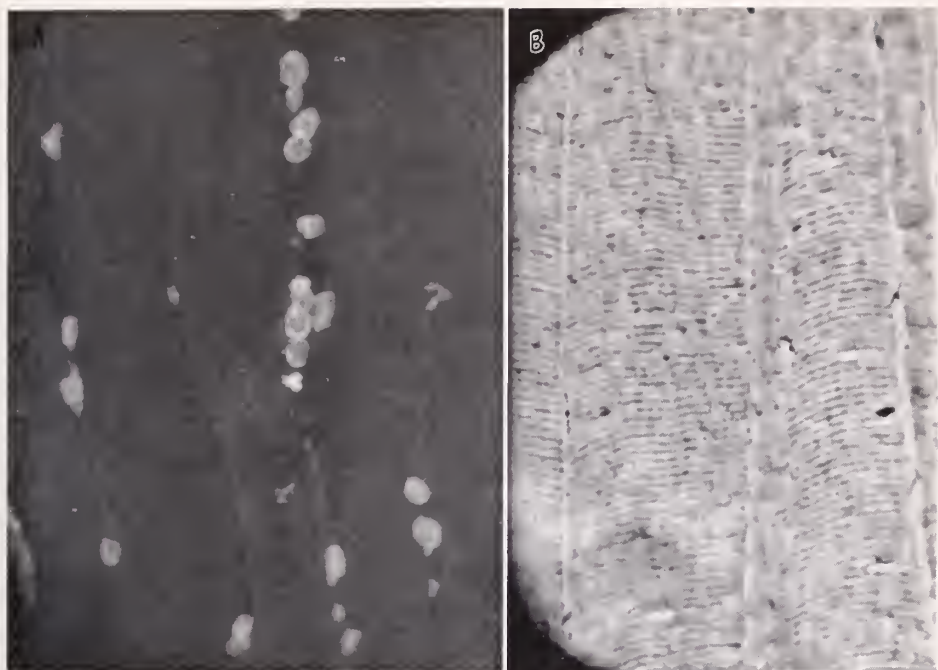


FIG. 2. Immunofluorescent Staining of Skeletal Muscle. *A*. Negative reaction showing no striations, but does show antinuclear factor; *B*. Positive reaction showing striations. Indirect methodology with serum diluted 1:60.

antibody findings in each group. Significant hemagglutination titers were found in a number of sera from myasthenics without thyroid disease (23 of 41 with titers 1:250 and greater). Immunofluorescent antibody findings, in this group of hemagglutination positive sera, were present in only 20 of 41 (48.8%), whereas, in sera of patients with myasthenia gravis and thyroid disease, immunofluorescent antibody findings were present in 15 of 18 (83.3%) hemagglutination positive sera. Not all hemagglutination positive sera demonstrate immunofluorescent antibody findings (i.e. there is no strict correlation between the two serologic tests). This study confirms that the hemagglutination test is more sensitive in detecting thyroglobulin antibodies. The higher hemagglutination titer correlated with finding of immunofluorescent antibodies also. This is evident in sera from myasthenics with concomitant thyroid disease.

DISCUSSION

Thyroid disease has long been associated with myasthenia gravis, but in most reports this association has been with hyperthyroidism. Estimates of frequency of occurrence of hyperthyroidism in myasthenic patients vary from 3% to 8.8% depending upon the series reported (4-9). In this study, 5.3% of patients were found hyperthyroid at any given time in the course of their myasthenia. The total number of patients with thyroid disease and myasthenia gravis was 13.1% of which 5.7% were hypothyroid. Association of myasthenia gravis and

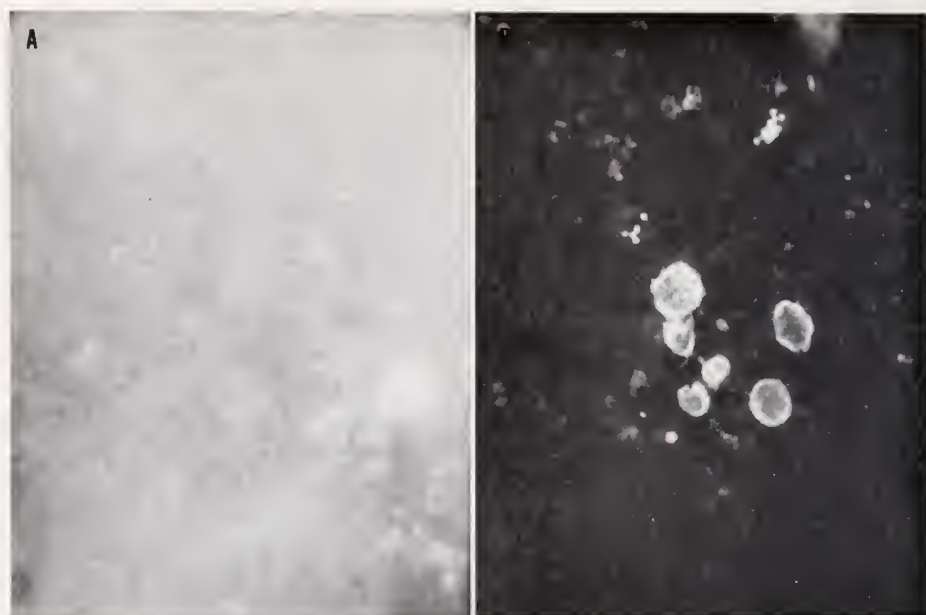


FIG. 3. Immunofluorescent Staining of Thymus Tissue. A. Negative reaction. Ghosts of two epithelial ? cells may be seen; B. Positive reaction. A group of six epithelial ? cells can be seen. Indirect methodology with serum diluted 1:60.

TABLE V

Hemagglutination Positive Sera Containing Immunofluorescent Thyroid Antibodies

Hemagglutination titer	Myasthenia without thyroid disease		Myasthenia with thyroid disease	
	Pt. total	+ Immunofluorescent antibodies	Pt. total	+ Immunofluorescent antibodies
Negatives (including 1:5 titers)	120	16 (13.0%)	21	2 (9.5%)
Positives				
1:25	18	5	3	2
1:250	10	4	6	4
1:2500	10	8	5	5
1:25,000	3	3	2	2
1:250,000	0	0	1	1
1:2,500,000	0	0	1	1
Total Positives	41	20 (48.8%)	18	15 (83.3%)

hypothyroidism has been a relatively infrequent finding in the literature (13, 20-22). Sahey et al (3) in a series of 260 cases of myasthenia gravis reported that eight patients had associated thyroid disease, five hypothyroid and three hyperthyroid. Sahey's is the only series, along with this study, in which hypothyroidism is found to be more frequently associated with myasthenia gravis than hyperthyroidism. Hyperthyroidism was evident clinically and confirmed

by laboratory testing. In this series, hypothyroidism was determined by laboratory testing and was not as evident clinically. Sahey's group points out that hypothyroidism is more likely to be overlooked clinically than thyrotoxicosis, thus there may be some cases in our group of 94 non-evaluated patients in which thyroid dysfunction was present but not suspected.

Two myasthenics with a histologic diagnosis of Hashimoto's disease were found in this series. Findings of histologic chronic thyroiditis in myasthenics have been reported (23, 24). Becker et al (25) noted changes suggestive of Hashimoto's disease in six of 32 patients (19%) with thyroid disease from postmortem cases of myasthenia gravis compared to 0.9% in a control group. Wolf et al (13) had not observed clinical evidence of thyroiditis, but found evidence at autopsy in some myasthenics. Daly and Jackson (26) reported a clinical case of Hashimoto's disease in which myasthenia gravis developed two years later. In his case, as in one Hashimoto's disease patient in this study, hemagglutination titer of 1:5–1:2,500,000 and a positive precipitin test was found; both tests are considered diagnostic for this disease. In our other case of Hashimoto's disease, a low hemagglutination titer and negative precipitin test were found. This has been reported by others in Hashimoto's disease (18, 27) illustrating variability of antibody titers in the disease. In an unpublished series of approximately 500 cases of thyroid disorders at Cornell Medical College (28), it was observed that approximately 20% of Hashimoto's disease cases had negative hemagglutination titer and upwards to 50% had titers in the range of 1:5 to 1:250. In this immunologic study of sera from 200 myasthenic patients, the majority of positive hemagglutination titers were in the low range of 1:25 to 1:2500 (see Table V).

The precipitin test was utilized specifically to determine if any of these patients could be suspected of having Hashimoto's disease. The test, if positive is considered diagnostic for Hashimoto's disease. But positivity may be found in only 60 to 65% of patients. It is infrequently positive (less than 2%) in other forms of thyroid disease with goitre (18). No myasthenic sera with low hemagglutination titers demonstrated precipitin antibodies. In two sera from middle-aged female myasthenics (one hypothyroid with goitre and one hyperthyroid) having hemagglutination titers of 1:25,000 and 1:250,000, precipitin antibodies were present, indicating perhaps that two more patients in this group may have Hashimoto's disease. Both patients had immunofluorescent antibody findings to muscle, thymus and thyroid tissue.

Recent reports describing multiple type of antibodies in sera from myasthenics have raised a number of questions as to their significance. Many have reported antithyroid antibodies in myasthenics. Van der Geld et al (10) found antithyroid antibodies in 36 sera of 111 patients (32.4%) using Coons and Kaplan's immunofluorescence technique (29) and in 9 of 81 patients (11.1%) using Boyden's tanned-red-cell hemagglutination test (30). Other studies: Adner et al (11)—35.3%; Simpson et al (12)—33%; Wolf et al (13)—16.6%; Sturgill et al (14) and Djanian et al (15) also reported findings of antithyroid antibodies. These reports make no mention of the clinical thyroid status of the

myasthenic patient nor of any allied disease in which there may be a generalized increase in antibody activity.

In 350 sera studied by the immunologic technique, antibody activity was correlated with the clinical status of the patient. Myasthenic sera demonstrated a significant amount of antithyroid antibody present primarily by the tanned-red-cell hemagglutination method. Analysis of Table II shows 114 myasthenics without any thyroid or allied disease of which 16.7% had immunofluorescence and 24.6% had hemagglutination antibody findings. In addition, 13.2% of these sera demonstrated both antibodies. To determine if these thyroid antibodies were significant, i.e. a representation of a generalized autoimmune process rather than a nonspecific finding, this group was compared to a normal one of similar average age and those representing a random mixture of relatively "non-antibody" producing diseases. It is suggested that thyroid antibodies found in some sera of myasthenics are a manifestation of an autoimmune process. This view is particularly supported by the finding of immunofluorescence antibodies to thyroid, thymus and muscle in 12.7% of sera from euthyroid myasthenics as compared to 0% in normal controls. Ninety per cent of this small group represented patients with a more severe and generalized form of myasthenia gravis (Groups II B, III and IV). Weiner and Osserman (2) have shown this to be true with muscle and thymic antibodies.

Concomitant thyroid disease probably accounts for the higher percentage of antithyroid antibodies in earlier reports mentioned above. In comparing sera from myasthenics and non-myasthenics with thyroid disease, a fairly good correlation of thyroid antibody activity occurred in both groups as shown in Table III. While presence of thyroid antibodies in the myasthenic-thyroid group does not imply a causal relationship, it does not preclude that these diseases in some instances may be the result of a similar autoimmune process. These findings confirm the clinical association of the two entities. Demonstration of thyroid antibody findings in the other categorized groups (Table II) suggests increased antibody activity as a result of thyroid disease process, subclinical thyroid dysfunction or a nonspecific finding which has no significance on disease in question. Since circulating antithyroid antibodies have been described in many normal middle-aged people, especially females (over 10% in one series of 1297 patients), (31) it is possible a small number of myasthenics without concomitant disease have nonspecific antithyroid antibodies.

This study suggests multiple antibody production occurs in sera of myasthenic patients since muscle and thymic as well as thyroid antibodies are found. Why some myasthenics have a particular tendency to develop antibodies to many organ systems is unknown. It is suggested that clinical myasthenia gravis may represent different immunologic types in a generalized autoimmune process resulting perhaps from a breakdown of immune tolerance and may be operative in some patients affecting specific organ systems with common antigens. This hypothesis has been advanced and supported by other investigators (10, 12, 32, 33). It is also possible that antibodies found are a result of the disease process rather than etiologic in nature.

SUMMARY

Eight hundred one myasthenia gravis patients were studied for thyroid disease: 105 patients (13.1%) had a concomitant thyroid disorder; 5.7% hypothyroid, 5.3% hyperthyroid and 2.1% with nontoxic goitre. Two patients had Hashimoto's disease confirmed by histologic findings and two were suspected of this as the result of clinical and immunologic testing.

Sera of 200 of 801 myasthenia gravis patients and 150 controls were studied by immunofluorescence techniques for antibodies to striated muscle, thymus and thyroid tissue, and by tanned-red-cell hemagglutination test for antithyroid antibodies. The precipitin test was performed on sera from 75 myasthenics with and without thyroid disease. Correlations between immunofluorescent antibodies and clinical thyroid status were made on all 350 sera tested. In 39 patients with myasthenia gravis and thyroid disease, sera of 41% had positive immunofluorescence findings and 46% had positive hemagglutination titers as compared to 52% and 51% respectively in serum controls with similar thyroid disease only. In 114 patients with myasthenia only, sera of 16.7% had positive immunofluorescence results and 24.6% had significant hemagglutination titers as compared to only a small percentage in normal controls. Previous reports of 30 to 35% antithyroid antibodies in sera from myasthenics were probably due to concomitant thyroid disease. A significant number (12.7%) of sera from euthyroid myasthenics demonstrated immunofluorescent antibodies to muscle, thymus and thyroid substrates suggesting multiple antibody production secondary to a generalized autoimmune process affecting organ systems with possible cross-reacting antigens.

Hypothyroidism and hyperthyroidism appear to occur at variable times during the course of myasthenia gravis and seem to be associated with the more severe myasthenic states.

Acknowledgments

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Intussusception in Acute Lymphoblastic Leukemia

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Leukemic involvement of the gastrointestinal tract is well known. Although gross lesions are rare, microscopic infiltration are found in about 13% of cases at necropsy. These changes are seldom associated with clinical symptoms. The case described herein is one of the few reported in which symptomatic intussusception was the presenting feature of acute lymphoblastic leukemia.

CASE HISTORY

A 36-year-old white man was admitted to The Mount Sinai Hospital, New York, for the evaluation and treatment of acute lymphoblastic leukemia and possible colonic neoplasm. Three weeks prior to admission, he developed crampy lower abdominal pain. Occult blood was found in the stool and the peripheral blood smear showed a high percentage of immature cells. An enlarged spleen was palpated. Barium enema performed in another hospital had shown ileocecal intussusception without obstruction. One week prior to admission, there was onset of bleeding from the gums and one episode of epistaxis that persisted for two days. In the abdomen, a slightly tender 6 by 8 cm mass was noted in the right paraumbilical area which moved with respiration. There were enlarged cervical and inguinal lymph nodes. Hepatosplenomegaly was noted. The white count on admission was 18,600 cells per cubic millimeter, with 66% blasts. The platelet count was 3,000 per cubic millimeter. Bone marrow findings were compatible with acute lymphoblastic leukemia. On barium enema examination (Fig 1A), a lobulated, smooth intraluminal filling defect was seen in the ascending colon (multiple upper arrows). The right colon was shortened and there was evidence of intussusception with "spring coiling" proximal to the lobulated mass lesion. There was no ulceration within this mass. The terminal ileum entered at the most inferior part of the intussusception and though participating in the intussusception was not dilated. Pressure spot films (Fig 1B) showed the mass and the intussusception in better detail.

Various entities were considered in the roentgenologic differential diagnosis of this patient. An independent carcinoma of the ileocecal valve producing the intussusception was considered but the lack of obstruction was surprising. Lymphosarcoma was thought to be less likely because of its rarity in a patient with acute leukemia. On the other hand, a leukemic tissue mass was a definite possibility. Benign lesions of the ileocecal valve such as lipoma or myoma with intussusception were not seriously considered because of lobulation and erased mucosa.

The patient was treated with various chemotherapeutic agents, but progres-

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FIG. 1A. A lobulated mass of the ileocecal region lies in the ascending colon (*upper arrows*). Although the mucosa in this region is effaced no obvious ulceration is seen. "Coiled spring" appearance typical of intussusception is observed (*lower arrow*). There is no small bowel obstruction. FIG. 1B. Spot view of same region shows the mass and intussusception in greater detail.



FIG. 2. Arrows point to the elevated submucosal lesion found at ileocecal junction.

sive deterioration occurred. The abdomen became severely distended. Bright red blood was removed on abdominal paracentesis. The patient expired in hemorrhagic shock in spite of repeated blood transfusions. The clinical diagnosis was acute blastic leukemia and neoplasm of the cecum with intussusception. The total length of the illness was six weeks.

NECROPSY EXAMINATION

Postmortem examination revealed extensive subcutaneous hematmata over the abdominal wall, penis and scrotum. The abdominal cavity contained 2500 cc of fresh blood. The spleen was markedly enlarged and weighed 1600 grams. Its follicles were obscured. The liver twice normal size and weighed 2600 grams. The cut surface showed pale white dots diffusely scattered throughout the liver parenchyma. The mesenteric lymph nodes were conspicuously enlarged and had greyish red gelatinous cut surfaces. At the ileocecal junction an elevated submucosal lesion measuring 5 by 2.5 cm produced partial intussusception of the ileum. The mucosa covering the tumor mass was intact. The mass had a greyish white fish flesh cut surface with hemorrhagic streaks. The tumor was firm and nodular (Fig 2).

MICROSCOPIC EXAMINATION

The portal tracts of the liver appeared prominent with clusters of predominantly lymphoid and mononuclear cells and occasional blast forms. These cells

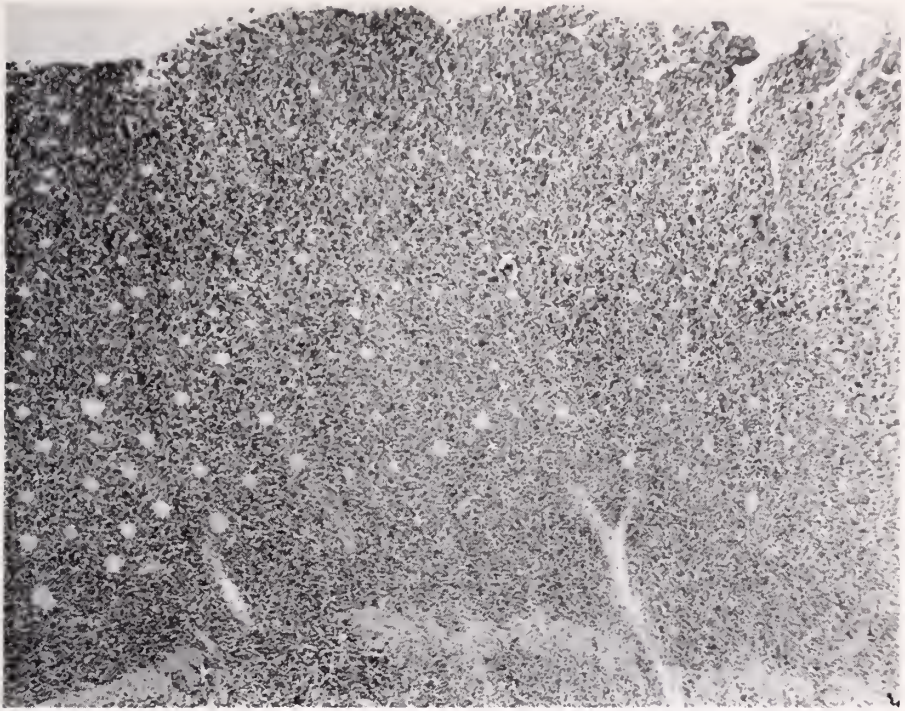


Fig. 3. Microscopic section of the lesion showing compact sheets of lymphoid cells.

were also in the sinusoids of the liver but to a lesser degree. The spleen cords were distended by a similar type of cell population. The lymph nodes had lost their normal architecture. The germinal centers were absent. The follicles were replaced by lymphoid cells of uniform shape. Areas of hemorrhage were scattered throughout the nodes. The tumor at the ileocecal junction was composed of compact sheets of lymphoid cells with scant cytoplasm (Fig 3). Hemorrhagic areas were seen in the tumor. (The final anatomic diagnosis was acute lymphoblastic leukemia with leukemic infiltration of the ileum and tumefaction at the ileocecal junction leading to ileocecal intussusception. The cause of death was massive intraabdominal hemorrhage.)

DISCUSSION

Clinical manifestations of gastrointestinal tract involvement in acute leukemia are rare. Even more so, is the patient in whom these manifestations are the presenting symptoms. The case described in this article combined both of these rare features. Intussusception was initiated by localized leukemic infiltration of the bowel wall, forming a lesion which radiologically resembled a malignant epithelial growth. The first similar case in the literature is mentioned by Hoffman in 1905 (2). Sinclair (3) in 1920 published another case of acute lymphoblastic leukemia associated with intussusception. In this latter instance,

the initiating lesion was a polypoid growth in the upper ileum showing microscopically reactive hyperplasia of the lymphatic tissue. Thompson (4) described a case in a four year old girl who had acute intussusception of the small bowel requiring resection. The resected bowel showed necrosis and hemorrhage. Acute lymphatic leukemia was diagnosed a week later. Recently Feldman (5) has described an additional case of lymphoblastic leukemia and intussusception caused by intramural hematoma of the small bowel. One might argue from the pathological and clinical picture that this case should be interpreted as leukosarcoma. A white blood count never rising above 30,000 might be explained as invasion of lymphosarcoma cells into the blood as a consequence of a diffuse lymphosarcoma. Goldberg and Emanuel (6) have reported similar microscopic findings in their series of diffuse lymphosarcoma simulating lymphatic leukemia. From the hematological standpoint, however, the predominantly blastic picture in the bone marrow in this case would not be compatible with a leukosarcoma. It is surprising that although infiltration of the bowel wall is common in acute leukemia, the complication described here is so rarely seen. Possibly, the short survival of patients with acute leukemia reduces the incidence of this occurrence. With increasing effectiveness of chemotherapeutic agents, prolonging the life of patients, the clinician may more frequently encounter similar gastrointestinal tract complications. Intussusception caused by leukemic infiltrate or intramural hematoma should be considered in the differential diagnosis of abdominal symptoms in acute leukemia.

SUMMARY

A patient with acute lymphoblastic leukemia is described who had ileocecal intussusception caused by localized leukemic infiltrate of the bowel wall.

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Bacterial Drug Resistance: Current Perspectives

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The occurrence of drug resistance in experimental and clinical tuberculosis is a well established fact, and it may suffice to state that practically all antituberculous agents are able to select resistant mutants in vitro and in vivo. There exist quantitative differences; the mutagenic properties and their selective potencies differ in degree, and some compounds, e.g., ethambutol [(+)-2,2'-(ethylenediimino)-di-1-butanol] Shepherd et al (1) cause slow emergence of mutants of comparatively low resistance. Moreover, the availability of an appreciable number of active compounds makes it possible to combine drugs with different modes of action in order to avoid lack of activity owing to cross resistance. These facts and experiences are so well known that it may be permissible to limit this report to a discussion of the problem of prevention of drug resistance and the possibility of overcoming of manifest resistance. It will be necessary to approach these questions from a general point of view and to refer to observations made in studies with other microorganisms and which may not apply to *Mycobacterium tuberculosis* at the present time.

PREVENTION OF DRUG RESISTANCE

Ehrlich's discovery of the phenomenon of drug resistance in 1907 was followed by two recommendations for avoiding the occurrence of fastness. The first was based on the concept of the ideal chemotherapeutic effect *therapia sterilisans magna*, i.e. the total elimination of pathogens in the infected host by an adequately large dose of an effective compound. This effect has been observed in experimental trypanosome or spirochetal infections of rodents, but was never found in natural infections with these or other protozoal or bacterial organisms. The only exception is the penicillin treatment of gonorrhea. It is true that the standard dose of penicillin is not always satisfactory in some cases and a certain degree of reduced sensitivity may be found, although it may not always be demonstrable by the sensitivity test in vitro. However, resistance comparable to the sulfonamide resistance of earlier periods is extremely rare and Ehrlich's early postulate is probably valid.

The specificity of action of compounds of different chemical structures and their different binding sites and biochemical mechanisms of action led to Ehrlich's second suggestion, namely, the combination of two or more drugs with different modes of activity. In this case mutants resistant to one of the compounds may be eliminated by the action of the second or third compound.

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Basically the present therapy of tuberculosis represents the practical application of this principle. The result is a suppression or delay of resistance, but also the emergence of organisms insensitive to one, two, or three drugs. This situation necessitates the continued search for new drugs effective in infections with *M. tuberculosis* either alone or as a replacement of the adjuvant drugs.*

TERMINATION OF DRUG RESISTANCE

Although pure clones of resistant organisms may retain their resistance indefinitely, a spontaneous and experimental return to sensitivity is possible in mixed populations. Owing, for instance, to the higher reproduction rate of sensitive members of the population the number of resistant mutants can decrease, particularly if the exposure to the selective pressure of a mutagen is discontinued. Drug sensitivity is a genetically determined property which can be transmitted by DNA of the sensitive strains or by phage-mediated transduction (2, 3). The possibility of breaking or reducing manifest bacterial drug resistance by exposure to chemical agents could not be demonstrated by reproducible methods for a long time. Only recently has it been shown that certain forms of resistance can be eliminated by exposure to acridine dyestuffs such as acriflavine or acridine orange.

TRANSMISSIBLE (INFECTIOUS) MULTIPLE DRUG RESISTANCE

This form of resistance, known for about ten years, is found mainly in gram-negative organisms of the enteric and genitourinary tract (*E. coli*, *Klebsiella*, *Shigella*, *Salmonella*, *Vibrio cholerae*, *Proteus*). These organisms have been first found in Japan (4, 5) in *Sh. flexneri*, *E. coli*, and *S. typhimurium* which were resistant to four chemically unrelated agents, namely sulfonamides, streptomycin, chloromycetin, and tetracycline. More recently also additional resistance to penicillin (ampicillin) (Anderson and Datta [6]) and kanamycin-neomycin (Lebek [7]) has been described. Datta (8) mentions a strain of *S. typhimurium*, from Canada, resistant against sulfonamides and six different antibiotics. Multi-resistant strains have been found with increasing frequency in many different parts of the world. Datta (8) stated that the number of organisms resistant to one or more antibiotics increased from 2.5% in 1961 to 18.7% in 1963-1964; the resistance of most of these isolates could be transferred to the sensitive *E. coli* strain K12. Watanabe's data (5) indicate that the frequency of resistant *Shigella* increased in Tokyo from 3.2% in 1957 to 11.8% in 1959 and reached 52.1% in 1960. Similar figures were obtained in Nagoya and Osaka. Kabins and Cohen (9) in this country found 24% multiple transmissible resistance among 72 strains of *Shigella*. Smith (10) isolated eight resistant *Salmonella* strains from 32 patients. Seven of these organisms were resistant to more than one antibiotic, and three were resistant to three or four drugs, namely streptomycin.

* There exist no antimicrobial drugs against which drug resistance cannot be obtained. It may, however, be mentioned that there are a few organisms in which resistant mutants are absent or extremely rare, *Entameba histolytica* and *Treponema pallidum*.

tetracyclines, ampicillin, sulfonamides. Similar studies by Gill and Hook (11) showed that the drug fastness of 25 out of 254 isolates of *Salmonella* resistant to chloramphenicol (or ampicillin), tetracycline, streptomycin, and sulfonamides was transmissible to K12 strain of *E. coli*. In twenty instances the entire set of R-factors was transferred.

The wide range of chemically unrelated antibacterial substances involved in this phenomenon is unusual and not within the familiar pattern of cross resistance. Moreover, this form of drug fastness cannot be transferred by cell-free filtrates and is not identical with the classical chromosomal type of resistance which possesses as a rule a high degree of specificity. Transferable resistance is furthermore characterized by the fact that other genetic markers, e.g. serological type, biochemical and nutritional (10) properties are not transferred.

The transfer of the various resistance (R-) factors and resistance transfer factors (RTF) from one bacterial host to another is achieved by conjugation of resistant donor strains and sensitive recipient strains in vitro and in vivo. Establishment of a phenotypic expression of the recipient strain occurs in vitro rapidly within minutes, but the resistance can be of long duration, although loss of fastness has been observed. Transfer of resistance has been demonstrated in human volunteers (4), in mice, using either germ-free animals or known methods of intestinal sterilization (12), and in the sterile intestinal tract of newly hatched chicks (14). The transmission can be demonstrated after 24 to 48 hours. The degree of resistance of the different organisms to the various antibacterials can show considerable variations, but 50 to 100-fold resistance and even higher degrees of fastness have been observed. It has been mentioned before that the phenomenon of multiple infectious drug resistance occurs most frequently in gram-negative organisms of the intestinal and genitourinary (15) tract, but is studied in staphylococci with increasing frequency. Mitsuhashi et al (16) described multiple resistance of two staphylococcal strains to tetracycline, sulfonamides, penicillin and three macrolides of the erythromycin group. Resistance could be transferred by transduction by phages. Only the resistance to the erythromycins was sensitive to acriflavine. Richmond (17) and McDonald (18) also emphasized the phage-mediated transduction in antibiotic-resistant hospital strains of staphylococci which also carried a marker of resistance to mercury compounds. Recent studies by Novick and Morse (19) describe the successful transmission of transducible erythromycin resistance and penicillin resistance of *Staphylococcus aureus* in vivo using the renal staphylococcal infection in mice. By selecting as recipients mutants with chromosomal resistance to streptomycin or streptomycin and novobiocin, the authors obtained strains with triple or quadruple patterns of fastness.

The mechanism of resistance is, as in other forms of drug fastness, dependent on the drug. In the case of the tetracycline factor it may be change of permeability (20), and in the case of the ampicillin resistance, it is destruction of the drug by penicillinase (6).

THEORETICAL ASPECTS

It should be mentioned that not all R-factors are transmissible, and in Anderson's theory it is assumed that two factors are involved in the transferable resistance, namely the R-factor as the resistance determinant and the transfer factor (RTF) (see Anderson and Lewis [21]). It is not possible to discuss here all theoretical aspects of the phenomenon of transferable multiple resistance. It may suffice to point out that the R-factors are considered cytoplasmic extrachromosomal genetic elements, similar to episomes. The term episome signifies, according to Jacob and Wollmann (22), an added genetic structure introduced in a bacterium from external sources by conjugation or transduction. These "genetic elements may either be present or absent. They control, therefore, genetic properties which are dispensable" (*ibid.*, p. 319). The term episome has been applied to certain phages, and it is apparently not entirely applicable to all R-factors. Lederberg (23) prefers the expression "plasmid."

This brings to mind another episomal factor, the fertility factor (F-factor) of certain cells of *E. coli* which transmit the fertility agent to other *E. coli* cells by conjugation (24, 25). It is not without interest that there exists an antagonism between the F-factor and the R-factor (see Watanabe [5]). Certain R-factors inhibit the F-factor.

One specific property of the F-factor deserves our interest, namely its sensitivity to acridines. It shares this characteristic with the R-factors.

ELIMINATION OF RESISTANCE (CURING OF R-FACTORS)

The episomal or plasmidal multiple resistance of bacteria also shows the sensitivity to nonbacteriostatic concentrations (26) of acridines, particularly acriflavine, to a lesser degree to acridine orange (4). Although not all R-factors are equally sensitive, it is possible to eliminate manifest resistance by a short exposure to acriflavine. UV irradiation can enhance the effect of acridines.

Not all R-factors are sensitive to acridines; also the frequency of reversal to sensitivity can show considerable variations, e.g. from 4.2 to 100% in *Shigella* strains (27); still lower frequencies (1 to 3%) have been observed. Mitsuhashi et al (26) found that multiple resistance can be more sensitive to acriflavine than the fastness to a single drug.

The elimination of multiple resistance has been demonstrated only in vitro so far. It would be desirable to approach this problem also by animal experimentation which is technically not difficult. The result of a clinical study by Sharda et al (28) may offer an indication that an attempt to eliminate resistance in vivo may be justified. These authors treated urinary infections caused by drug-resistant organisms (*E. coli*, *K. aerogenes*, *Proteus*, enterococci, streptococci) with chloramphenicol, sulfonamides, or nitrofurans combining the individual drugs with the antimalarial acridine compound quinacrine; they obtained sterility of urine in 8 out of 10 cases. The authors

TABLE I
Multiple Drug Resistance

Antibiotic	Multiple Resistance		
	In Gram-negative Organisms*	In Staphylococci	
		Natural*	Experimental
Chloramphenicol.....	+	—	+
Kanamycin-Neomycin.....	+	—	nt
Streptomycin.....	+	—	+
Penicillin (Amp).....	+	+	+
Sulfonamides.....	+	+	nt
Tetracycline.....	+	+	+
Erythromycins.....	—	+	—

* Transmissible.

nt = not tested.

based their treatment methods on Sevag's experiments (29) which had shown that the combination of the nonbacteriostatic quinaerine with antibiotics (streptomycin, penicillin, tetracycline, chloramphenicol, erythromycin, novobiocin) prevented the emergence of resistant mutants of *E. coli* and staphylococci. In one instance Sevag observed sensitivity to streptomycin (1000 $\mu\text{g/ml}$) in a highly resistant strain of *E. coli* when a high concentration of quinaerine was present. It is, however, not evident that quinaerine can "cure" R-factors, although this possibility deserves consideration.

ORIGIN OF TRANSFERABLE RESISTANCE

The cause of the emergence of multiple infectious resistance has not yet been elucidated; Watanabe (4, 5) believes that the exposure to one or more antibiotics or other antibacterial agents may have been brought about "by RTF in a single step from the host chromosome of an unknown bacterium." Anderson and Lewis (21) discuss the possibility that the resistant organisms may have originated in antibiotic-treated livestock. Indeed, Smith and Hall (30) and Walton (13) isolated from feces of pigs, calves and fowls, strains of *E. coli* with the characteristics of transmissible multiple resistance towards ampicillin, streptomycin, tetracycline, chloramphenicol, neomycin, and occasionally furazolidone.

In this connection it may be well to remember the experimental work of Fusillo (31). He exposed staphylococci to a single antibiotic after "pre-selection" on a medium which allowed hardly any growth (nonglucose sulfite agar); he obtained mutants which showed multiple resistance to chloramphenicol, tetracycline, streptomycin, and penicillin. The similarity of this pattern of resistance to that exhibited by the enteric bacteria is remarkable (see the Table), but, understandably, nothing is known about the transfer of resistance of these organisms.

PERSPECTIVES

Watanabe (5) mentioned that some form of experimental approach should be available in order to produce infectious resistance at will and to study some of the still unanswered questions. It does not seem inconceivable that experimental arrangements like the one described by Fusillo (31) or similar procedures could be devised thus allowing further elucidation of the problem of the origin of this form of resistance and the perhaps even more fascinating problem of the elimination of resistance. The occurrence of episome-mediated multiple resistance may well be a more frequent event involving other genera and species of organisms. Mycobacteria should not be excluded from such consideration particularly with regard to the area of "primary" resistance in untreated patients.

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UNUSUAL PROBLEMS IN SURGERY

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CASE NO. 7

Hydatid Cyst of Liver With Abscess, Rupture, Empyema and Broncho-hepatico-cystic Fistula

Echinococcus disease of the liver is rather commonplace in certain parts of the world but in the United States the disease is so rare that no institution has acquired a vast clinical experience with it (1). As infestation generally occurs in childhood, the period of close contact with dogs and poor appreciation of personal hygiene, the average primary cyst is almost as old as the patient. The liver is the commonest site (74%) with the right lobe more frequently affected than the left (4 to 1). In 75% of the cases the cyst extends toward the abdominal cavity, while more than one cyst is present in about 25% of cases. The outstanding clinical feature of the uncomplicated cyst is its latency, even large cysts being compatible with apparently perfect health. Pain is rare and pressure effects are uncommon. Daughter cysts are present in most adult cysts and many show slight biliary contamination and peritoneal adhesions. These too, are latent, although epigastric discomfort, mild nausea, distension, and vomiting are common.

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It is the complications which cause a dramatic change in the clinical picture and prognosis. Seventy percent of patients first present themselves because of some complication which is always associated with some degree of leakage or rupture of the cysts (2). In order of importance the complications are: intrabiliary rupture; suppuration; intraperitoneal rupture. The following case is presented to illustrate the protean manifestations of the complications and the problems of diagnosis and treatment.

CASE REPORT. The patient is a 33 year old white male, born in Yugoslavia, who had been residing in New York City for seven years working as a mechanic. While under treatment for a duodenal ulcer at another hospital in 1961, a routine chest x-ray revealed some abnormal finding and a diagnosis of tuberculosis was considered a possibility. He subsequently had chest x-rays taken on three occasions but no definite diagnosis could be made and the patient was discharged. An appendectomy was performed 15 months prior to admission to Elmhurst City Hospital Center. Eight months prior to admission he went to Europe where he was hospitalized because of abdominal pain radiating to the right upper quadrant, fever and chills. His temperature ranged as high as 105 degrees F. Serum transaminase and stool study for ova and parasites were normal as were roentgenograms of the gall bladder and urinary tract. After one month he was discharged with the diagnosis of subacute cholangitis. He continued to have intermittent severe epigastric pain radiating to the R.U.Q. and right shoulder.

On January 5, 1966, the patient was admitted to the medical service of Elmhurst



Case No. 7, Fig. 1. Chest x-ray taken day of first admission. Only elevation of the right diaphragm is seen. Chest is clear.

because of severe abdominal pain, fever, chills, anorexia, and a weight loss of 40 pounds in the preceding three months. The fever began several days before admission and was associated with diarrhea and increased severity of the abdominal pain. He was a moderate cigarette smoker and did not drink alcoholic beverages.

PHYSICAL EXAMINATION. The patient appeared toxic and complained of abdominal pain. There was no respiratory distress. Temperature was 103 degrees F; pulse, 100/min;

respiratory rate, 22/min; blood pressure, 110/60 mm Hg. Examination of the throat, heart and lungs was not remarkable. The abdomen was soft, and not distended. There was severe tenderness over the liver which was firm and enlarged extending to 6 centimeters below the right costal margin. No other organs were palpable. The bowel sounds were normal. Rectal examination was normal.

LABORATORY STUDIES. Laboratory studies disclosed the following values: hemoglobin,



Case No. 7, Fig. 2. Liver scan January 1966. Massively enlarged liver pushed down with diminished uptake in right lobe.

10.3 gm/100 cc; hematocrit, 33%; white blood count, 9,900 with 49 segs, 9 bands, 37 lymphocytes, 4 monocytes and 1 eosinophil; blood urea nitrogen, 12 mg/100 cc; glucose, 94 mg/100 cc; amylase, 52 units; alkaline phosphatase, 4.2 to 7.9 Bodansky units; bilirubin, 1.1 mg/100 cc; and total protein, 7.9 grams (alb. 3.3, glob. 4.6). Liver function studies included cephalin flocculation, 3 plus, thymol turbidity, 8 units, and serum transaminase within normal range. Electrolyte studies of sodium, chloride, potassium and CO_2 were normal. Serologic test for syphilis was negative. A blood culture yielded no growth. Stool studies did not show ova or parasites. A chest x-ray in inspiration and expiration revealed normal bilateral diaphragmatic motion. The right diaphragm was elevated but there was no evidence of effusion or active parenchymal disease in either lung (Fig 1).

The diagnosis considered most likely was subphrenic abscess. Also mentioned was liver abscess, either amebic or echinococcal. The

patient was treated with intravenous penicillin and tetracycline in high doses. Chloroquine was begun two days after admission and chloramphenicol was added several days later. The fever subsided over the next five days and there was progressive diminution of the abdominal pain. A liver scan (Au^{198}) was interpreted as demonstrating a massively enlarged liver that appeared to be pushed downward and to the left. The superior and lateral portion of the right lobe showed markedly diminished uptake consistent with a diagnosis of extrahepatic lesion displacing the liver or a lesion replacing this portion of the liver, such as a cyst (Fig 2). Sigmoidoscopy revealed no pathology. On Jan 25, 1966, the patient was presented at surgical grand rounds and the three possible diagnoses considered were: intrahepatic abscess of amebic origin; hydatid cyst of the liver; and space occupying mass of the right lobe of the liver. The consensus of opinion favored an exploratory laparotomy preceded by further studies to prove the presence of



Case No. 7, Fig. 3. Chest x-ray, April 1966. Sharply outlined mass above an elevated right diaphragm with fluid level. Broncho-cyst fistula suspected.

amebiasis or hydatid disease. At this time, however, the patient signed himself out of the hospital against advice.

He was not heard from until he reported to the screening clinic at Elmhurst on April 11, 1966 and was readmitted because of cough and expectoration. He stated that he had been feeling quite well, gained weight, and was afebrile. In recent weeks he began to have a severe coughing spell for about 10 minutes every few days with expectoration of yellowish material that later became a dark chocolate color. He appeared well nourished and in no acute distress. The temperature was 99 degrees F, and the pulse, respiration, and blood pressure were normal.

There was diminution of breath sounds

with dullness to percussion over the right lung base. The liver was not clinically enlarged at this time. Routine blood counts, hemoglobin, serum transaminase, alkaline phosphatase and serum bilirubin were all within normal limits. A chest x-ray again demonstrated elevation of the right leaf of the diaphragm. Above the right diaphragm there was a sharply outlined mass which moved negligibly on respiration. Lucent areas were seen in the mass-like density which changed their position in a decubitus film, indicating the presence of fluid and air in a cavity (Fig 3). The x-ray findings were interpreted as a large suprahepatic or intrahepatic abscess contiguous above with an extrapleural mass within the right chest. Com-

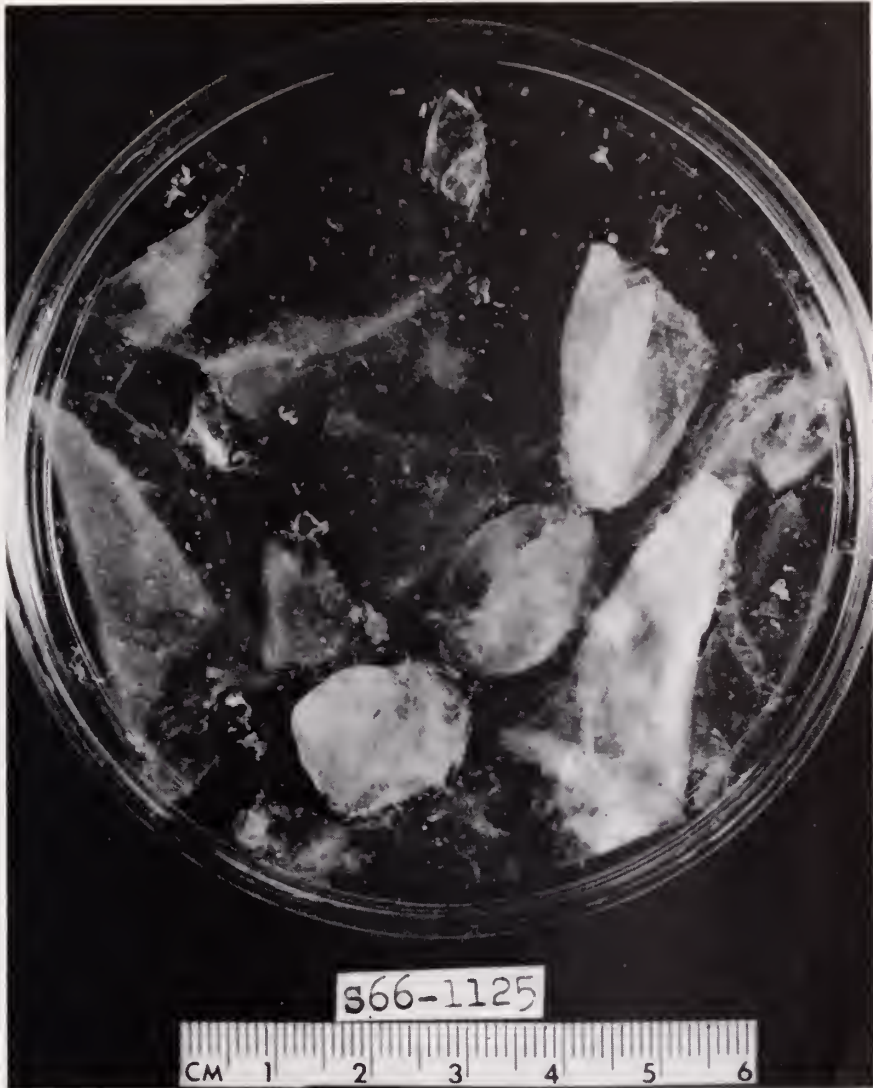


Case No. 7, Fig. 4. Postoperative chest x-ray after drainage of empyema. Cavity has shaggy wall and contains air. Note small air-fluid level below diaphragm. No pneumothorax.

munication with a bronchus was suspected. A liver scan at this time showed less displacement and more uniform uptake in the liver.

The patient coughed up 8 to 10 ounces of chocolate colored material for several days after admission. No ova or parasites were detected in the sputum. A sputum culture grew out *S. viridans*. No amebae were seen in the stool. The most probable diagnosis considered was a bronchohepatic fistula originating from an amebic abscess or a rup-

tured echinococcus cyst. The thoracic surgeon believed that the cavity was extrapulmonary and a thoracotomy was recommended. On April 15, 1966, a 4 inch length of the posterior portion of the ninth rib was resected subperiosteally using local xylocaine anesthesia. Thick purulent material was aspirated through the bed of the resected rib. An incision was made into the empyema cavity which was surrounded by a thick fibrous wall and was loculated. The

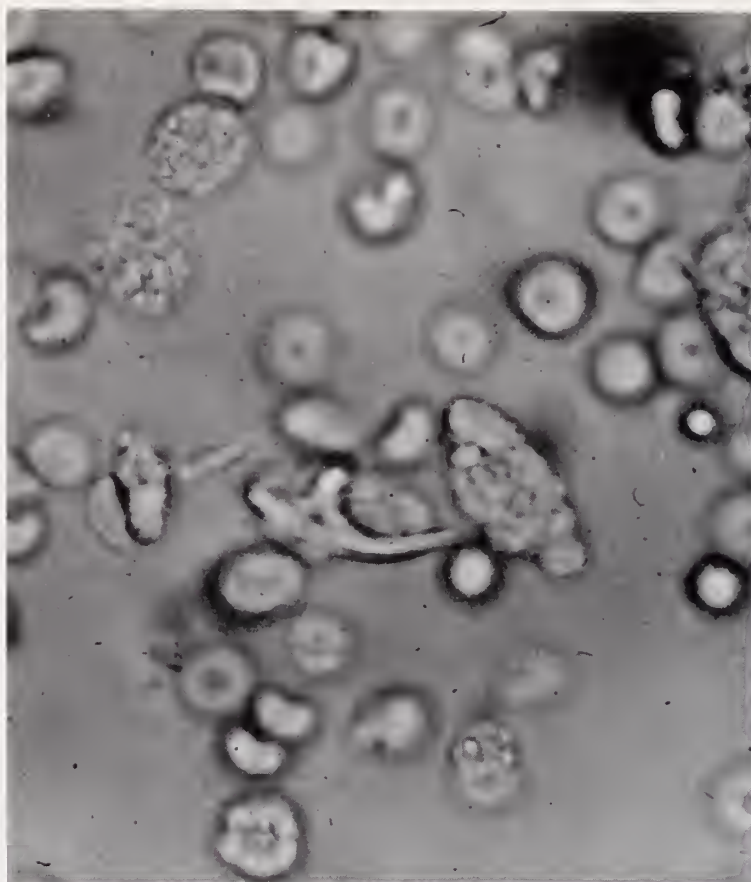


Case No. 7, Fig. 5. Specimen removed from empyema cavity shows filmy membranes of daughter cysts.

contents evacuated included grossly purulent material and a viscid fluid containing cyst-like structures measuring 0.5 to 5 centimeters. A large latex tube was placed in the cavity and the wound was closed loosely using chromic gut for muscle and silk for skin. A postoperative chest x-ray exhibited no signs of pneumothorax or hemothorax. The mass at the base of the right lung ap-

peared to have a shaggy wall and contained air. An air-fluid level was demonstrated below the right diaphragm which was suggestive of a subdiaphragmatic collection or residual fluid in the cavity which was drained (Fig 4).

The postoperative course was benign. The chest tube drained a small amount of sero-sanguinous fluid containing some necrotic



Case No. 7, Fig. 6. Microscopic appearance of hooklet in centrifuged empyema content.

material. Serial chest x-rays indicated that the cystic mass was gradually diminishing.

Pathologic study of the filmy cystic structures revealed the typical appearance of echinococcal daughter cysts some of which were lined with a layer of gram negative rods (Fig 5). The centrifuged fluid showed many hooklets in the unfixed sediment (Fig 6).

On April 26, 1966, 11 days after the empyema drainage, a right thoracotomy was performed through the bed of a resected portion of the tenth rib. Aspiration below a thickened hemorrhagic tissue representing the diaphragm yielded purulent material. The posterior portion of the diaphragm was sutured to the parietal pleura to prevent contamination of the general pleural cavity

which was not infected by the previously drained localized empyema cavity. An incision through the diaphragmatic tissue disclosed the presence of an abscess secondary to a perforated, infected hydatid cyst, the size of a large grapefruit, located in the right lobe of the liver. This was directly subjacent and adherent to the diaphragm. The liver abscess was thus the primary pathology which had eroded the diaphragm and caused the empyema cavity. The process had also eroded into a bronchus thus producing the broncho-hepatico-cystic fistula. The cavity was irrigated with saline followed by ether. Two latex tubes were inserted into the infected cyst and the cyst capsule was closed snugly around the tubes and partially



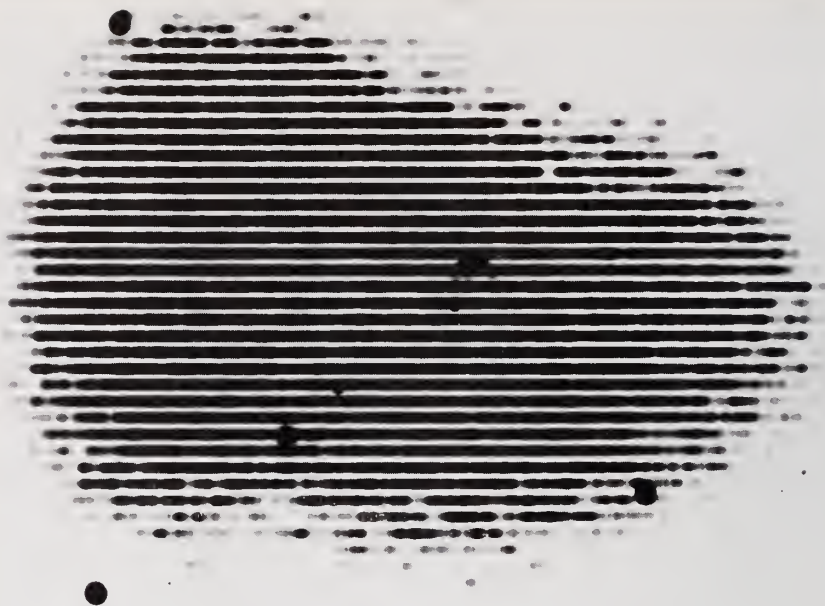
Case No. 7, Fig. 7. Contrast medium outlines the shrunken intrahepatic abscess. Biliary tree was also visualized.

sutured to the diaphragm. The diaphragm was then sutured to the intercostal tissues near the incision and the chest wall was closed leaving the tubes to emerge from the center of the incision.

Pathologic study showed a chronically inflamed echinococcus cyst wall as well as hooklets in the sediment.

The postoperative course was afebrile and uncomplicated. An upright chest x-ray taken on the fourth postoperative day showed no air in the abdomen beneath the right hemidiaphragm thus indicating that there was no communication with the general peritoneal cavity. The drainage from the intrahepatic tubes was bile stained and remained stabilized at approximately 200 cc per day. A

culture revealed the presence of *Aerobacter aerogenes* and *S. aureus*, coagulase positive. The drainage from the empyema tube ceased after several days but air continued to pass because the bronchopleural fistula had not yet closed. No antibiotics were administered since the infectious process was locally isolated and drainage was adequate. Two weeks after the second operation the patient was ambulatory with a plastic bag attached to collect the intrahepatic drainage. On May 18, 1966 contrast medium was instilled into the intrahepatic abscess and a roentgenogram demonstrated considerable shrinkage of the cavity which communicated with the biliary tree (Fig 7). A similar technique using the empyema tube showed diminution



Case No. 7, Fig. 8. Liver scan taken one month after drainage of hepatic abscess shows no filling defect, as before, in the right upper aspect.

of the cavity and a communication of the cavity with the lower lobe bronchial tree. A small linear tract of contrast medium extended from the lower limit of the empyema cavity to the upper portion of the sub-diaphragmatic abscess cavity. It was not possible to distinguish whether this represented a communication between the two cavities or an opacified bronchial trunk. A liver scan taken May 24, 1966 showed a more homogeneous uptake than previously with no filling defect, as before, in the right upper aspect of the liver (Fig 8). The broncho-pleural fistula closed about one month after the hepatic abscess was drained and the empyema wound healed rapidly. The patient was discharged from the hospital June 6, 1966 with one intrahepatic tube in place. He was seen every week or two in the outpatient clinic where the drainage became negligible and the final drainage tube was removed in August, 1966. Chest x-ray taken in June, 1966 showed further resolution of the chest pathology (Fig 9). All wounds

were completely healed by the latter part of August, 1966. The patient was not heard from until June, 1967. When he was interviewed at that time he stated that the wounds had healed completely by September, 1966 and that he had returned to full time work at that time. He appeared robust and was entirely asymptomatic. The chest examination was normal except for slight dullness at the right base due to some permanent residual fibrosis. A chest x-ray was normal except for some cloudiness at the right base and minimal obliteration of the right costophrenic sinus secondary to the former disease and surgical intervention which healed leaving some residual fibrosis (Fig 10).

DISCUSSION. Surgical eradication of hydatid disease is the only form of curative therapy since nothing of a medicinal nature has as yet been found to have a significant effect in the treat-



Case No. 7, Fig. 9. Chest x-ray 2 months after drainage of hepatic abscess shows considerable resolution of chest pathology.

ment of hydatid infestation. In the 19th century tapping operations were usual (3). Indeed, the suppuration which occurred following repeated tapings frequently destroyed the cyst; however, due to lack of adhesions between the cyst and the parietes, the tapping would lead to leakage into the peritoneal cavity with widespread dissemination of the disease and hopeless

chance for cure. Saenger introduced the concept of cautious marsupialization of hydatid cysts by securing the cyst to the lips of the external wound before making the incision into it (4). Formolage was introduced by the French surgeons based on the fact that a weak formalin solution will kill scolices and fix brood capsules within a few minutes (5). Subsequent im-



Case No. 7, Fig. 10. Chest x-ray 14 months after surgery. Slight cloudiness of right base and minimal obliteration of costophrenic sinus. No sign of active disease.

provements in technique included the obliteration of the sac space usually around a drainage tube after removal of the endocyst and its contents, or by filling the cavity with omentum.

The case presented here exhibited signs and symptoms which were all compatible with the diagnosis of hydatid disease and yet he was treated at various times for duodenal ulcer, cholangitis and appendicitis. The diagnosis was unduly delayed because of

unawareness of the possibility of echinococcus infestation, even in Yugoslavia, where the patient was hospitalized for one month.

During his first admission to Elmhurst, there was no sign of any thoracic extension of the disease; there was suppuration but the cyst had apparently not ruptured. The exploratory laparotomy recommended at that time may have been all that was necessary to eradicate the disease. How-

ever, an abdominal approach would have entailed the risk of spillage and dissemination. As it turned out, although the disease progressed to rupture and localized empyema, the primary abscess was evacuated at the most favorable site where it was adherent to the diaphragm, through the bed of the tenth rib, thus avoiding the contact of the cyst contents with either the general peritoneal cavity or the general pleural cavity. Although the complications in this case were ominous and rather widespread, the patient was fortunate in that his disease was localized by adhesions and could be adequately drained without disturbing any of his vital organs. His complete recovery without any signs or symptoms more than one year after surgery does not guarantee that he may not have a recurrence after a further prolonged period. However, there is a fairly good chance that the suppuration may have destroyed all viable germinal elements of the disease.

SUMMARY. A case of hydatid cyst of the liver complicated by suppuration, rupture, empyema, and bronchohepaticocyst fistula is presented. Surgery was performed in two stages using the bed of the ninth and tenth ribs respectively to drain the empyema and the cyst of the liver, and the patient has remained asymptomatic for more than one year. A brief review of the evolution of the surgical treatment of hydatid cyst of the liver is presented.

—*Julius Leichtling*

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CASE NO. 8

Lung Hernia

Posttraumatic herniation of the lung through an intercostal space is an uncommon occurrence. Fewer than 300 lung hernias of all types have been reported to date (2-9). The following case is an example of a lung hernia which developed after blunt trauma to the chest.

CASE REPORT. A 2 year old Colombian male was admitted to the Pediatric Surgical Service at Elmhurst Hospital in September of 1966 after having fallen to the pavement from a second floor window. There had been no loss of consciousness.

PHYSICAL EXAMINATION. The patient was well nourished, well developed and alert. The pulse rate was 100 beats per minute, blood pressure 100/70 mm Hg, respiratory rate 28 per minute and temperature 99°F. There were several small abrasions of the left anterior chest and lower abdomen. A well-demarcated area in the left sixth intercostal space at the anterior axillary line bulged on expiration (Fig. 1) and retracted on inspiration (Fig. 2). At this site a 2 by 6 cm defect could be felt in the intercostal muscles (Fig. 3). The child was in no respiratory distress. The trachea was midline and the breath sounds were normal. No other injury was evident.

LABORATORY DATA. The hematocrit value was 33%, the leukocyte count was 10,550. The urinalysis was within normal limits. Roentgenograms of the skull, abdomen and pelvis



Case No. 8, Fig. 1. Expiration. Hernia protrudes in sixth left intercostal space.

Case No. 8, Fig. 2. Inspiration. Depression is seen in sixth intercostal space.

Case No. 8, Fig. 3. The defect in the intercostal muscles is demonstrated.

demonstrated no abnormality. X-ray films of the chest revealed widening of the left sixth intercostal space and protrusion of the lung through the defect (Fig 4). There were

no rib fractures. The heart and lungs were normal.

COURSE. The diagnosis of rupture of the intercostal muscles with herniation of the lung



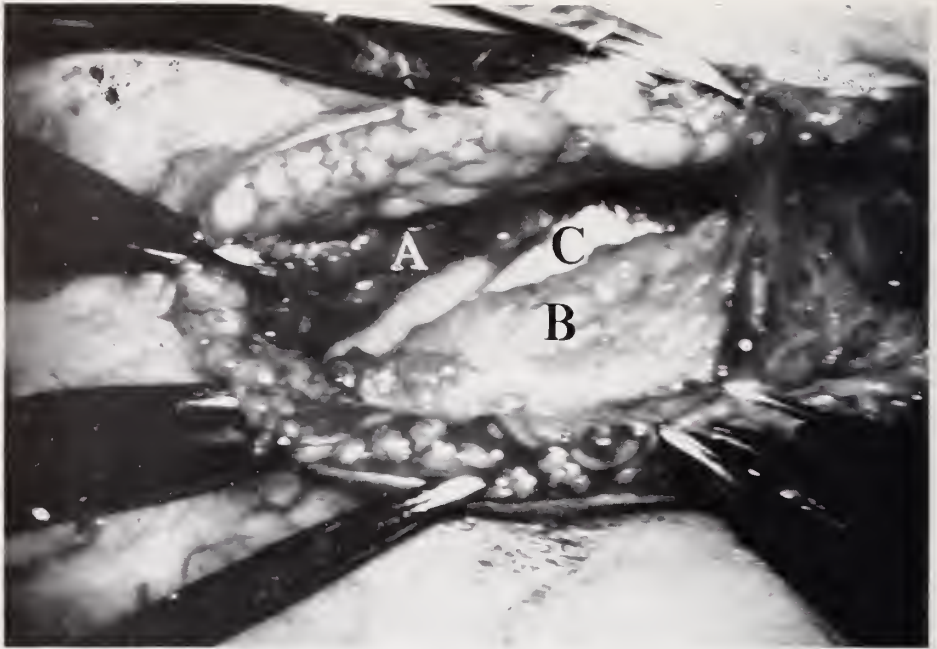
Case No. 8, Fig. 4. Chest x-ray following injury. Note extracostal lung shadow (arrow). There are no other abnormalities.

was made. The hernia was reduced and a bulky dressing was placed over the defect. Subsequent x-ray films showed no extracostal lung tissue. The patient was observed during the next 48 hours and no other injuries became apparent.

The hernia was repaired on the seventh hospital day using endotracheal anesthesia. A small left posterior lateral thoracotomy incision was made. Upon incising the skin and subcutaneous tissue an 8 cm defect through the lateral aspect of the intercostal

muscles and parietal pleura was seen. Remnants of the intercostal muscles were attached to both upper and lower ribs (Fig 5). There was no lung contusion or rib fracture. The defect was closed using pericostal sutures of chromic catgut. The intercostal muscles and skin were closed in layers after judicious debridement. A single intercostal catheter was used for underwater drainage.

The patient tolerated the procedure well. The postoperative course was uncomplicated and the chest tube was removed after 24



Case No. 8, Fig. 5. Operative photograph. Skin and subcutaneous tissue have been incised. A. upper rib, B. lower rib, C. lung. Parietal pleura and intercostal muscles have been torn.

hours. Follow-up x-ray films showed complete expansion of the left lung and narrowing of the sixth left interspace. Follow-up examination and x-ray films nine months after surgery revealed a well child with a solidly healed wound and no evidence of hernia recurrence.

DISCUSSION. A lung hernia may be defined as a protrusion of pulmonary tissue beyond its normal confines through an abnormal opening in the thoracic cavity. Herniation of one lung through the mediastinum to the opposite pleural cavity is therefore not included in this discussion. Although a true lung hernia must have intact parietal as well as visceral pleura, Ballinger (1) states that the presence of intact parietal pleura is of academic interest only and considers those cases

with disruption of the parietal pleura to be lung hernias. Lung hernias may be classified according to location or etiology (1).

I. According to location

- A. Thoracic
- B. Cervical
- C. Diaphragmatic

II. According to etiology

- A. Congenital
- B. Acquired
 - 1. Traumatic
 - 2. Secondary to local disease
 - 3. Spontaneous

In a collective review of 258 cases in 1963 (3), thoracic hernias comprised 65% of the series and cervical hernias

35%. Only one case of diaphragmatic herniation of the lung has ever been recorded (2). Congenital hernias accounted for 18% of cases, traumatic 52%, secondary 1% and spontaneous 29%. The majority of thoracic hernias follow an injury to the chest (1, 3) and may appear immediately or months or years following trauma (3, 5, 10). These hernias are seen in association with fracture of ribs, falls from heights, stab wounds, war wounds, crushing injuries and thoracotomy incisions (1, 3, 10). The hernia usually develops at the site of injury but occasionally a sharp blow to the chest may cause lung tissue to protrude through a preexisting area of weakness in the chest wall that is remote from the point of impact (9). The latter are commonly seen near the sternum or the spine. These two sites are the weakest portions of the intercostal spaces; the internal intercostal muscle extends posteriorly only to the angle of the rib while anteriorly the external intercostal muscle stops at the costochondral junction. Beyond these points there is only a thin connective tissue sheet, the anterior and posterior intercostal membrane which preserves continuity. The space is protected posteriorly by strong overlying muscle masses, whereas anteriorly, the weak point is protected only by the relatively ineffective pectoral muscles. Thus hernias develop more commonly in the anterior thoracic wall than posteriorly (1). Cervical hernias present as supraclavicular masses which protrude through the superior aperture of the thorax in the interval between the sternocleidomastoid and scalenus anticus muscles. Herniation usually occurs following some tear or deficiency in Sibson's fascia which nor-

mally limits cervical excursion of the dome of the pleura (7). Most congenital hernias of the lung present in the cervical region (1).

Some disagreement exists in the classification of congenital and acquired spontaneous hernia of the lung. This arises from the fact that a congenital weakness may exist for years until some undue strain causes the hernia to appear. Such hernias are seen later in life in people such as glassblowers or trumpet players whose occupation requires forced expiratory movements (1). A hernia may develop when the thoracic wall has been weakened by a local pathologic process, such as infection of the chest wall, breast neoplasms, empyema necessitatis, tuberculosis of the ribs and fungal diseases of the chest wall (1, 7).

Symptoms are few and vague (3). Occasionally there may be local tenderness or slight dyspnea (1). Strangulation is rare but, if present, signs of localized inflammation are seen (7). The diagnosis may be made by the presence of a soft crepitant protrusion which is reduced in size on quiet respiration and bulges forth on coughing, forced expiration or Valsalva maneuver. A defect in the chest wall may sometimes be palpated.

The diagnosis may be confirmed radiographically by the demonstration of extracostal pulmonary tissue on tangential exposures of the chest. The differential diagnosis includes tumors of the chest wall, subcutaneous emphysema, tuberculosis of the ribs, empyema necessitatis and gas gangrene.

TREATMENT. True hernias of the chest wall rarely heal spontaneously. The treatment is surgical unless some contraindication exists. Such operations

as simple closure of the defect (4), fascia lata grafts, and Ivalon (10) or Teflon patches have been used.

In their report describing the repair of eleven hernias of the lung, Maurer and Blades make the following points. Many defects of the chest wall which are associated with hernias of the lung will become increasingly rigid, but the hernia, although smaller, will persist and therefore should be repaired. They believe that the most important principle in the repair of a lung hernia is covering the defect with bone or periosteum which will produce bone. Any defect of the chest wall, regardless of size, can usually be repaired by plastic procedures involving only structures which are part of the chest wall; ribs, periosteum and muscle (7).

The most satisfactory repair of an average sized defect is obtained by suturing of periosteal flaps developed from ribs immediately above and below the margins of the hernial orifice (7).

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CASE NO. 9

Abdominal Pain and Shifting Masses

The following case illustrates one aspect of a disease which is rarely seen in this part of the country, but has been widely reported throughout other parts of the world.

CASE REPORT. A 24 month old Colombian born male was admitted to the Pediatric Surgical Service at Elmhurst Hospital because of abdominal pain. The pain began 12 hours prior to admission and was followed by vomiting of yellowish material and then diarrhea. The pain was intermittent and crampy at first but was constant at the time of admission. The past history and review of systems yielded no significant findings.

PHYSICAL EXAMINATION. The patient was a well nourished, well developed male child in acute distress because of abdominal pain. His temperature was 99°F rectally and his pulse was 104 beats per minute. The skin and mucus membranes showed evidence of slight dehydration. Significant physical findings were otherwise limited to the abdomen which was soft and slightly distended. There was a tender putty-like mass palpable in the right upper quadrant of the abdomen and a similar mass in the lower abdomen occupying the mid and left lower quadrants. The abdomen was generally tender but there was no evidence of peritonitis. Rectal examination revealed the presence of some very soft

yellow stools. There were no masses palpable rectally.

LABORATORY DATA. The hemoglobin concentration was 11 grams per 100 milliliters and the hematocrit value was 34%. The white blood count was 11,600 with a differential count of 70 polymorphonuclear leukocytes, 24 lymphocytes, 2 monocytes, and 4 eosinophils. The urinalysis was within normal limits. Flat and upright x-ray films of the abdomen revealed a mass in the right lower quadrant (Fig 1). There were several dilated loops of intestine but no significant air fluid levels. A barium enema was performed in an attempt to clarify the diagnosis. The colon appeared to be normal. After evacuation of the barium there was reflux into the terminal ileum and a large number of round worms were outlined (Fig 2). Follow-up x-ray films taken twelve hours later showed masses of worms in both the left upper quadrant and the right midabdomen. Much of the small bowel was presumably filled with worms and possibly with fluid. No free air was seen.

COURSE. Initial treatment consisted of intravenous fluids and gastrointestinal decompression by means of a nasogastric tube. By the following morning, the child was completely asymptomatic, the nasogastric tube was removed, and oral fluids were given. The masses which were previously felt in the right upper and left lower portions of the abdomen were now present in the right lower and left upper quadrants. The child passed several ascaris worms during the first and second hospital days. On the third hospital day, a large mass of round worms was passed (Fig 3). After passage of the worm bolus, no further masses could be felt in the child's abdomen. A course of Antepar,* 1 gm per day for two days was then started. The patient was discharged and followed in the Out-Patient Clinic. On the last examination, there was no further evidence of ascaris in the stool.

DISCUSSION. *Ascaris lumbricoides* is a parasite which is found in all parts of the world but is most commonly seen in the tropics and subtropics (8). Large series of cases of surgical com-

plications due to round worm infestations have been reported from South Africa (6, 8), India, China, Korea (3), and Nigeria (1). In these areas from 70 to 90% of all patients are infested with round worms. The commonest manifestation of round worm infestation is the asymptomatic passage of ova or adult worms in the stool. However, it is not unusual for patients with massive worm infestations to develop pulmonary and intestinal diseases. Such complications as pneumonia and lung abscess, intestinal obstruction, biliary obstruction, liver abscess, pancreatitis, appendicitis, perforation of the bowel and diverticulitis have been reported (1, 3, 6, 8). *Ascaris* worms have been found in practically every portion of the body including the peritoneal cavity, fallopian tubes, and urinary tract (8). By far the most common complications of round worm infestation are those related to the gastrointestinal tract. The various clinical manifestations may be explained by the peculiar life cycle of the worm. The adult worm normally lives in the human small intestine where the fertilized female lays her eggs in great numbers. The eggs are passed into the stool and deposited in the soil. Embryonization takes 9 to 13 days. There is no intermediate host. The ova are swallowed, enter the human stomach, and pass on into the small bowel where the intestinal juices digest the covering membrane of the eggs and release the larvae. The larvae then burrow through the intestinal wall and enter the mesenteric lymphatics and venules. From here they reach the lungs by way of the liver and the right side of the heart. Further growth takes place in the lung capillaries. The worms

* Piperazine Citrate, Burroughs Wellcome, Co.



Case No. 9, Fig. 1. Plain film of abdomen showing dilated loops of intestine and abdominal masses.



Case No. 9, Fig. 2. Barium enema. Colon is normal. Large numbers of ascaris worms are seen in distal ileum.

then penetrate the pulmonary capillaries, enter the alveoli and migrate by way of the bronchioles, bronchi, and trachea to the epiglottis. Here they are again swallowed and pass on into the small intestine thus completing the cycle. The worms may enter the left side of the heart by way of the pulmonary capillaries, and thus reach almost any organ in the body. The life span of a worm is estimated to be approximately one year.

The most common abdominal manifestation of massive ascaris infestation is mechanical intestinal obstruction (6, 8). The usual mechanism is obturation of the lumen of the small bowel, usually the lower ileum, by an entangled mass of worms. A less common cause of obstruction is thought to be due to spasmodic contractions of the small bowel on a smaller mass of worms, producing a complete obstruction. It has been shown by Herriek and Emery



Case No. 9, Fig. 3. Bolus of worms passed by the patient on the third hospital day. Note barium within intestinal tracts of the worms.

(5) that ascaris may cause spasm of smooth muscle. Obstruction may also be caused by inflammation and matting of the loops of small bowel at the site of an ascaris worm. Secretions of worms are capable of provoking an inflammatory reaction (2), and toxic de-

composition products of disintegrating worms may even cause necrosis of the bowel wall (3). Other less common mechanisms of intestinal obstruction include volvulus, intussusception and obstruction by adhesive bands, all of which are precipitated by the presence

of masses of worms within the intestinal tract (3, 6, 8).

The clinical picture is dependent upon the mechanism of obstruction. In a series of 68 cases of intestinal obstruction in children caused by ascaris infestation (6), abdominal colic was present in all. Vomiting occurred in 90%; constipation was present in 54%; and 28% had watery stools. In most children, fever was low grade. The majority of children were not very ill, abdominal distention was slight or moderate, and tenderness was minimal and poorly localized. Single or multiple putty-like abdominal masses were present in two-thirds of the cases. They were present in all regions of the abdomen and characteristically were tender and changed in position, size and number. Eosinophilia varied from 5 to 25% but was not of diagnostic value as 80% of all children were infested with worms. Plain X-ray films of the abdomen usually revealed distended small bowel loops with scanty air fluid levels. A small number of children were acutely ill. Most of these patients had high fever, abdominal distention and localized tenderness, often with signs of peritonitis. Plain x-ray films of the abdomen in this group of children revealed many air fluid levels. These patients were submitted to urgent laparotomy.

In most cases the obstruction is incomplete and subsides rapidly after gastrointestinal decompression and intravenous fluid administration. In a small percentage of cases, however, a serious surgical emergency may arise. This situation occurs when worm infestation is complicated or accompanied by volvulus, intussusception, adhesive bands, or impairment of the

viability of the bowel. Louw (6) suggests that laparotomy be performed if the following symptoms and signs arise: 1. the passage of blood by rectum, 2. a very ill and toxic child with a tensely distended abdomen and rebound tenderness, 3. the presence of multiple fluid levels on abdominal radiographs, 4. unsatisfactory response to conservative therapy.

If surgery is undertaken the definitive treatment will depend upon the condition of the bowel. If the bowel is viable, then the bolus of worms should be fragmented and massaged onward into the cecum where the ascaris becomes powerless, possibly because of some digestive action of the large bowel. If fragmentation is not possible, the bowel may be opened and the worms removed (8). Some authors are of the opinion that the bowel should not be opened and a resection of the portion of the bowel containing the worms and an end-to-end anastomosis be performed (6). If the bowel is not viable then obviously a resection must be carried out.

Piperazine citrate is the drug of choice (7). The dosage is calculated on a weight basis and should be given once daily for two consecutive days. The treatment may be repeated if necessary after one week. It is important that no antihelminthics be given until severe symptoms have subsided, as dead and dying worms tend to impact in the lower ileum and produce a complete intestinal obstruction. In cases of partial obstruction which respond to conservative treatment, it is recommended that antihelminthics not be given until the child is asymptomatic. In those cases which are treated by laparotomy, antihelminthics should

not be started before the seventh to tenth day (8). Piperazine is effective in at least 95% of cases and since the drug induces a partial paralytic state in the worms, abnormal migrations of the adults do not occur (7).

—A. Robert Beck

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CLINICO-PATHOLOGICAL CONFERENCE

Malabsorption in an Elderly Male

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A 67 year old white man was hospitalized because of bloody diarrhea for one day. Four years previously he developed non-bloody diarrhea with abdominal cramps and a weight loss of sixty pounds. He was admitted to another hospital for treatment and remained well for three years. However, symptoms recurred which only partially responded to corticosteroid therapy, and he was admitted to The Mount Sinai Hospital. Physical examination was unremarkable except for midabdominal tenderness. The hemoglobin level was 12.7 gm/100 cc; the blood urea nitrogen, serum calcium, phosphorus and urine were normal. The total serum lipids were 555 mg/100 cc, total cholesterol 166 mg/100 cc and phospholipids 190 mg/100 cc. The serum carotene was 27 μ g/100 cc. After oral administration of vitamin A, the serum level rose from 85 μ g/100 cc to 147 μ g/100 cc in six hours. The fecal fat excretion was 14.2 gm per day. The fasting blood sugar was 71 mg/100 cc. A glucose tolerance test showed an insignificant rise in the blood glucose levels. He excreted 3.5 gm/100 cc of xylose in five hours following an oral load. The serum albumin was 3.5 gm/100 cc and globulin 2.0 gm/100 cc. Paper electrophoresis of the serum showed the gamma globulin fraction to represent 11.5% of the stainable protein. X-ray examination of the small bowel demonstrated an irregularly contoured column of barium through which the mucosal pattern could not be delineated. The distal jejunum and ileum were mildly dilated; the mucosal pattern was coarse and increased secretions were present. A jejunal biopsy was performed and corticosteroid therapy discontinued. He was discharged on a gluten-free diet with vitamin supplements.

Six months prior to his second admission he had an exacerbation of symptoms with bloody diarrhea. He was treated at another hospital with blood transfusions and ACTH and was discharged to a nursing home five and one half months later on prednisone, 15 mg per day, Kaopectate, vitamins and meprobamate. He regained approximately eight of the forty pounds he had lost during hospitalization and noted an improvement in appetite and well-being. On the day of admission he passed three bloody bowel movements, did not become diaphoretic and did not have chest pain.

At age 44 he was hospitalized for a lobar pneumonia and at 63 years of age was treated for an acute myocardial infarction.

He was a chronically ill man. The blood pressure was 100/58, pulse rate 88/min, respirations 16/min, and temperature 99°F. His heart and

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lungs were normal and no abdominal organs were palpated. The abdomen was slightly distended, but bowel sounds were normal. There was clubbing of the distal phalanges and mild ankle edema. Rectal examination revealed grossly bloody stool. The hemoglobin level was 11.9 gm/100 cc, the erythrocyte sedimentation rate 3 mm/hr, and the white blood cell count 9,100 with a normal differential count. The urine was normal, as was BUN, fasting blood sugar, serum electrolytes, calcium and phosphorus. The serum albumin was 2.3 gm/100 cc and the globulin 1.9 gm/100 cc. Electrophoresis of the serum demonstrated a decrease in all globulin fractions. The serum alkaline phosphatase activity was 11.7 King-Armstrong units and the serum glutamic oxaloacetic transaminase activity 13 units. The prothrombin time was 69 seconds (control, 12 seconds). The chest x-ray was normal and the electrocardiogram suggested an old lateral wall infarction.

Following intravenous vitamin K and blood transfusions the rectal bleeding subsided and the prothrombin time returned to normal. He was maintained on prednisone, testosterone propionate, vitamins and antidiarrheal agents, but he continued to have two to four watery bowel movements per day. During the second week of hospitalization he was noted to be icteric. The total serum bilirubin was 6.2 mg/100 cc with 4.2 mg/100 cc direct reacting. The serum alkaline phosphatase activity was 28 King-Armstrong units and the SGOT activity 64 units. He became anorectic and required tube feeding. A liver biopsy was performed. Increasing lethargy developed and neomycin therapy was begun. A serum ammonia reading was 3.1 mg/ml. Jaundice persisted with progressive deterioration of clinical condition. On the 44th hospital day he became hypotensive and the electrocardiogram showed an acute myocardial infarction. He died two days later.

*Dr. Janowitz**: When this man developed abdominal pain, cramps, diarrhea, and a loss of sixty pounds of weight, I suspect a neoplasm was considered the most likely diagnosis. Other diagnostic possibilities must have included inflammatory disease of the small or large bowel. However, he remained well. When his symptoms recurred three years later, he was treated with corticosteroids. What clinical entities were considered at this time that his physicians would treat with steroids? Malabsorption or malabsorptive symptoms are not usually treated with steroids unless one has something more specific regarding their nature. Nontropical sprue beginning at the age of 63 is rare, although Trevor Cook reported that his oldest patient was 63 years of age. While a lymphoma is possible, I have nothing to support the diagnosis. When he was seen a year before his death, the physical examination was not remarkable. Specifically, the liver and spleen were not felt and there were no lymph nodes. He had a normal hemoglobin level or at least he was only slightly anemic. Although many blood chemistry determinations were normal, there was evidence of malabsorption. The serum carotene level was low and the vitamin A level was slightly below normal and rose only moderately after ingestion of vitamin A. On a regular ward diet, he

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FIG. 1. Multiple dilated loops of small intestine.

excreted 14.2 grams of fat in 24 hours. The impaired glucose tolerance does not contribute to the diagnosis, since at least 25 per cent of the population have flat curves.

However, if he swallowed and retained the 25 grams of xylose given and excreted only 3.5 in five hours, he certainly had evidence of a generalized impairment of absorption of this pentose. It is interesting that his serum albumin and gamma globulin readings were normal since both congenital and acquired varieties of hypo or agammaglobulinemia may be associated with a malabsorptive syndrome. Could we see the x-rays of the stomach and the small bowel?

Dr. Present:* The upper gastrointestinal series showed multiple dilated loops of small bowel. The mucosa was effaced and there was increased fluid in the small bowel. No nodulations were present and there was no evidence of fistulization or a tumor mass (Fig 1). The terminal ileum was normal (Fig 2). The x-ray appearance of the small bowel suggested a malabsorptive state, but the abnormalities were nonspecific.

Dr. Janowitz: The x-rays certainly are not classical of the adult celiac disease characterized by feathering of the mucosa, dilatation, segmentation and moulage formation. With evidence of malabsorption, provided by the findings of steatorrhea, diminished xylose excretion, and some impairment of vitamin A absorption, I would like to be able to make etiologic diagnosis. A jejunum biopsy would be of great help.

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FIG. 2. Normal terminal ileum.

*Dr. Rybak**: A biopsy was performed one year prior to death and showed flattening of the mucosa with atrophy, clumping of the villi, and an abundant cellular infiltration in the lamina propria in contrast to the normal small intestinal villi which are long, slender, and covered by cylindrical epithelial cells (Fig 3).

Dr. Janowitz: Obliteration of the normal villus pattern, with fusion of the villi, and reduction in the size of the columnar cells is consistent with and characteristic of sprue, nontropical sprue, or adult celiac disease. The changes are by no means pathognomonic, since they can occur in a variety of conditions and are not necessarily the result of sensitivity to gluten. In addition, interference with the blood supply, and inflammatory changes in the small and large bowel can be associated with nonspecific sub-villus atrophy in the upper jejunum. However, the cellular infiltration of round cells suggests nontropical sprue. The physicians who took care of him must have considered this diagnosis in view of the three year history and his partial response to

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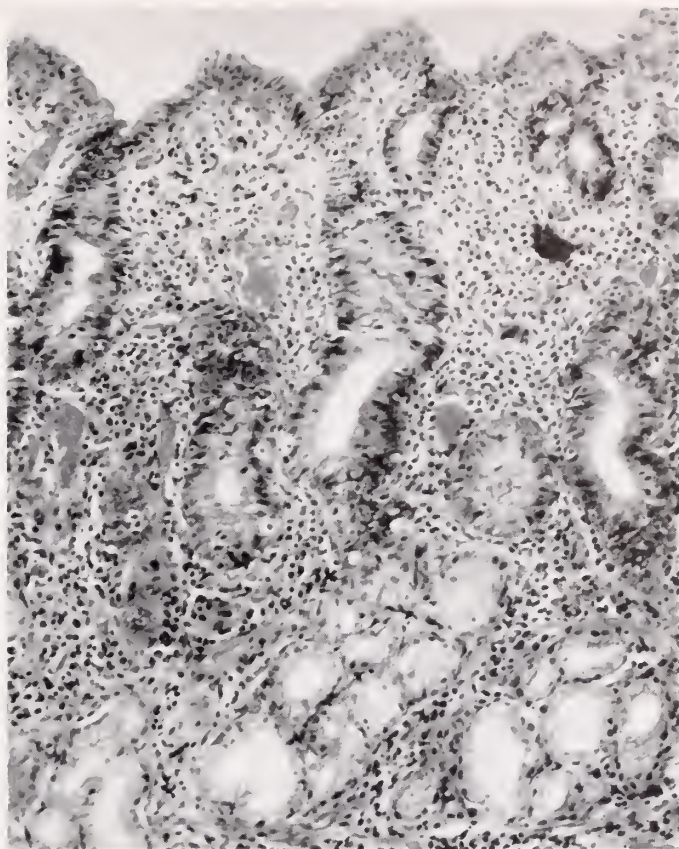


FIG. 3. Biopsy specimen of small bowel showing mucosal atrophy and cellular infiltration of the lamina propria ($\times 200$).

steroids. In addition, the response to a vigorous gluten-free diet also is significant. Although of every ten patients with sprue, eight or nine respond to a gluten withdrawal, the ninth may require withdrawal of lactose from the diet and the tenth may require steroids.

In any case, six months prior to his first admission to this hospital, the diarrhea became bloody. I was concerned about the presence of abdominal pain, since we usually think of the diarrhea of nontropical sprue as being painless. The combination of bloody diarrhea and malabsorption also is unusual. The anemia which resulted from malabsorption or blood loss was treated with blood transfusions. Because he had done well with steroids in the past, they were reinstituted. He improved clinically and regained about eight pounds. Prior to his final admission, he again developed bloody diarrhea. His general physical examination was unchanged, but he had clubbing of his fingers. Whether this was the result of small bowel or liver disease, I am unable to answer at this time. Tests of malabsorption were not repeated, but his serum albumin level was 2.3 gm/100 cc and his globulin 1.9 gm/100 cc.

Possibly, this was due to leakage from the gut as well as a failure of synthesis. Liver function tests were not remarkable, but prothrombin time was prolonged. In the absence of malabsorption of vitamin K, idiopathic hypoprothrombinemia is usually a factitious disease, from ingestion of Dicumarol by psychopathic individuals.

Vitamin K and blood transfusions corrected the abnormality and I assume the hypoprothrombinemia was due to steatorrhea and loss of fat soluble vitamins in the stool.

His response to a gluten-free diet was far from impressive. He was maintained on steroids, but failed to obtain a clinical remission. Something had apparently occurred in the course of four years. It has become apparent that patients with nontropical sprue may develop lymphosarcoma, reticulum cell sarcoma, or even Hodgkin's disease. Many patients have been described who have had nontropical sprue for long periods of time and then develop a lymphoma prior to their death. However, I am discouraged by the x-ray findings which do not show the characteristic nodularity of the mucosa.

Finally, the terminal episode appeared to be a combination of liver failure and an acute myocardial infarction. He developed anorexia, jaundice, lethargy, and progressive deterioration.

The serum ammonia was elevated, significant of the fact that some products of protein digestion in the intestine were either bypassing the liver or not being converted to urea. A liver biopsy was performed. Dr. Rybak, would you demonstrate the liver biopsy?

Dr. Rybak: A needle biopsy taken two weeks before his demise showed enlarged portal tracts containing proliferated ductules and inflammatory cells. The ductular proliferation extended into the parenchyma and some contained bile in their lumen. Large amounts of period-acid-Schiff positive material were found in the midzonal area, indicative of hepatocellular damage. In addition, there was marked centrilobular cholestasis (Fig 4). In summary, these findings are consistent with pericholangitis and severe cholestasis.

Dr. Janowitz: Unfortunately, I am unable to correlate the liver disease with a primary malabsorptive state of the small bowel. In addition, the biopsy failed to show evidence of lymphoma. Considering other possibilities to explain the malabsorption, one certainly has to think of Whipple's disease. However, macrophages were not seen on the jejunum biopsy, and the characteristic coccidial bodies, that Whipple had seen with a silver stain sixty years ago, were not found electron microscopically. Furthermore, while some of these patients do respond to corticosteroids, his course was too prolonged. Inflammatory disease of the small bowel, or regional enteritis, with or without involvement of the colon, would explain the bloody diarrhea, but neither the history nor the x-rays of the intestinal tract are compatible with this diagnosis.

The failure to find inflammatory changes high in the small bowel in typical regional enteritis is not surprising, since I have not seen granulomas in nonsurgical biopsies. What I have difficulty in explaining is the rather



FIG. 4. Percutaneous needle biopsy specimen of the liver. Portal tracts are enlarged by inflammatory exudate and proliferated bile ductules ($\times 40$).

nonspecific x-ray pattern of dilatation and loss of the normal mucosal pattern of the small bowel and the bleeding. Amyloidosis can cause gastrointestinal bleeding and malabsorption, but there was no evidence of amyloid on the liver or small bowel biopsy and there was no proteinuria.

I would like to consider one other diagnosis before I conclude my discussion. He was an elderly male with vascular disease, evidenced by a previous coronary artery occlusion. I wonder whether some of the changes in the small bowel and the malabsorptive syndrome may not have been due to mesenteric vascular disease. This could account for the abdominal cramps and the bleeding, as well as the malabsorptive syndrome. However, I have never seen a jejunum biopsy of a patient with mesenteric vascular disease with a malabsorptive syndrome and only can conjecture that his biopsy might be consistent with such a diagnosis. Therefore, I find myself in the same unhappy situation as the clinicians who treated this patient. There are features suggesting primary malabsorption and primary disease of the small bowel, which partially respond to steroids and gluten-free diet, but which really followed a progressively downhill course. I believe he had nontropical sprue, terminating in a lymphoma. I have considered amyloidosis, but feel it is unlikely. Finally, I considered mesenteric vascular disease as the basis for this malabsorptive syndrome since he was an elderly male with other evidence of arterial disease.

Dr. Rybak: At autopsy, the patient was deeply icteric and there was edema of the lower extremities. Two liters of clear yellowish fluid were present in the abdominal cavity and 1 liter in each pleural cavity. The

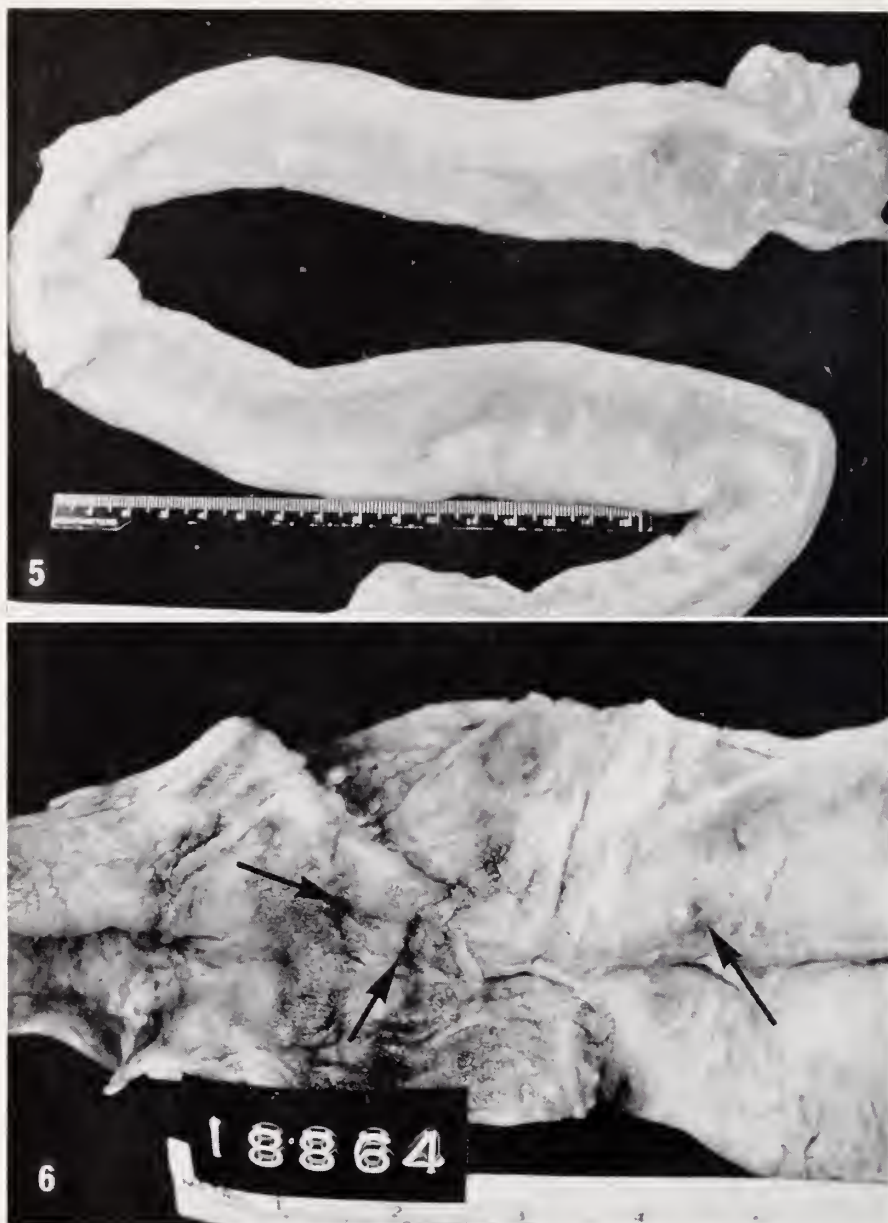


FIG. 5. Extensive mucosal atrophy of small intestine.
FIG. 6. Multiple punched out ulcers of jejunum (arrows).

mucosa of the small intestine was atrophic and the rugae were absent (Fig 5). Microscopically, the mucosa was flat and an abundant cellular infiltrate was present in the lamina propria. In the ileum the mucosa was flat, the villi absent, and the crypts elongated, dilated and infiltrated by

mononuclear cells. The bones were osteoporotic and consistent with a malabsorptive state. The spleen and lymph nodes showed extramedullary hematopoiesis and iron deposition. Superimposed on the atrophic small bowel mucosa, mainly in the jejunum, and sparing the terminal ileum were punched out ulcerations (Fig 6). The muscularis mucosa was interrupted and large numbers of inflammatory cells infiltrated the lesions. The inflammatory infiltrate consisted of plasma cells and an occasional polymorphonuclear leukocyte. The ulcers were of different ages. Some were fresh with hemorrhage into the mucosa and a gram stain showed bacteria in the necrotic crypts extending into the lamina propria.

The liver was markedly icteric and mottled on cross section. The extrahepatic biliary tree was normal. A connective tissue stain showed broad portal spaces with fibrosis extending out in a perilobular distribution. There was severe centrilobular cholestasis and mild fatty infiltration. Nodular formation and two-cell thick hepatic plates indicating regeneration suggested the liver lesions were not acute. What was the cause of the gastrointestinal bleeding? Dr. Himes, Gabriel and Adlesberg reported a 38 year old man who had primary malabsorption and severe gastrointestinal bleeding. At autopsy, numerous small intestinal ulcerations and erosions were found. One of them actually perforated the bowel. Dr. Klempner in 1937 presented a patient with diarrhea who developed increasing jaundice and died in hepatic failure three and half years later. He called the hepatic lesion "chronic intrahepatic obliterating cholangitis." Referred to now as pericholangitis with cholestasis, this complication is frequent in ulcerative colitis. Mistilis et al reported 441 patients with ulcerative colitis, 24 of whom had pericholangitis, diagnosed by liver biopsy.

In summary, the patient had a bleeding disorder associated with a low prothrombin time due to malabsorption. He developed mucosal hemorrhages which led to ulcerations and subsequent bacterial invasion. The latter probably led to a portal bacteremia and pericholangitis. We did not find an acute myocardial infarction, but rather an old myocardial infarction with occlusion of one of the branches of the left coronary artery. The patient died of a bronchopneumonia.

Are there any questions or comments?

Dr. Janowitz: Therefore, this patient developed nontropical sprue or adult celiac disease at the age of 63. While it is within our clinical compass to consider such a possibility, it certainly is not common.

The average age of onset of adult celiac disease is between 35 and 55 although it has been reported in the first and second year of life and as late as in the sixth decade.

When such a patient with nontropical sprue and primary malabsorption, or idiopathic steatorrhea deteriorates, one has to consider a variety of complications. I considered lymphomatous degeneration.

Whether steroids precipitate ulcerations has not been resolved. Certainly diffuse multiple ulcerations of the entire small bowel sparing the colon in

sprue is extremely rare. Dr. Rybak, you postulated the liver disease as secondary to bacterial invasion and portal bacteremia. Can you estimate the age of the ulcerations?

Dr. Rybak: The liver disease was chronic. In contrast, the intestinal ulcerations were both acute, probably agonal and chronic since they showed extensive fibrosis.

Dr. Janowitz: The older literature does not indicate a significant or characteristic change in the liver in sprue. The analogy with ulcerative colitis is interesting, but we lack significant information regarding the presence of liver disease associated with sprue.

Dr. Hans Popper:* I do not think the liver disease was directly related to sprue. In the untreated patient, fat is occasionally present; however, following treatment, the liver becomes virtually normal. Also no one truly knows the etiology of the liver disease found in ulcerative colitis. The histology suggests bacterial infection because of the leukocytic infiltration. However, this type of bacterial cholangitis, or pericholangitis, occurs very late in the course of ulcerative colitis. Why we do not get the same type of liver disease in such disorders, regional enteritis, or other diseases with septic ulcers is unclear. This is an unusual case of intrahepatic cholestasis, pericholangitis and small intestinal ulcerations.

Question: In nontropical sprue the albumin is usually low.

Dr. Janowitz: This patient had been on steroid therapy for years and we have seen reversion to normal in patients with sprue in moderate remission. However, I think a serum albumin of 3.5 gm/100 cc in this patient was abnormal, but slightly higher than expected because of the steroid therapy. The failure to respond to gluten withdrawal and to steroids and a persistent abnormal biopsy in an illness of three years duration again points out our lack of knowledge concerning the nature of primary malabsorption.

Final Diagnosis:

1. Nontropical sprue with small intestinal ulcerations
2. Pericholangitis and cholestasis
3. Osteoporosis
4. Extramedullary hematopoiesis
5. Coronary atherosclerosis with myocardial fibrosis

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RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D.

CASE NO. 291

A forty-three year old man was admitted to the hospital for evaluation of epigastric discomfort, dyspepsia and right sided abdominal pain. Multiple



Case 291, Fig. 1. Left-anterior oblique view from barium enema examination shows reflux of barium into terminal ileal loops. Terminal ileum is narrowed with irregular contours and frayed mucosa. There is separation of adjacent bowel loops indicating thickening of bowel wall and mesentery (arrow). There is no abnormality in the colon, including the caput cecum.

From the Department of Radiology, The Mount Sinai Hospital, New York, N.Y.



Case 291, Fig. 2. Posteroanterior post-evacuation film shows residual barium in ileum. The terminal two feet reveal changes characteristic of granulomatous ileitis. Margins of the bowel are hazy and ill-defined. There is no normal mucosa. The surface pattern is amorphous distally. Residual proximal folds are markedly thickened, blunted and irregular. There is a sharp transition to normal bowel in the left mid-abdomen.

abdominal complaints had been present for many years. Gastrointestinal series performed six years prior to admission was said to have revealed marked duodenitis and G. I. series performed three years prior to admission was said to have been normal. (These studies were not available for review.) A bloody stool was passed three years prior to admission, exact character not determined. Six months ago a G. I. series was again performed and the duodenal bulb and second portion of the duodenum were noted to be abnormal. Three months prior to admission the patient developed sharp, colicky right lower quadrant pain. There was no fever or diarrhea. The pain did not respond to symptomatic medication but persisted until the time of admission.

Past history included a diagnosis of gout and the passage of uric acid gravel five years prior to admission. Subsequent intravenous pyelogram was said to be normal. The patient has been maintained on Benemid since that time.



Case 291, Fig. 3. Lateral view of stomach and duodenum from G.I. series shows marked thickening of folds in proximal duodenum. The descending duodenum is narrowed over a 4 cm segment. No ulcer crater is seen. The stomach shows no abnormality.

Barium enema examination revealed no colonic abnormality. Reflux into terminal ileal loops demonstrated the characteristic changes of granulomatous enteritis (Fig 1, 2). G. I. series revealed no abnormality in the esophagus and stomach. The duodenal bulb showed marked thickening of the folds. The second portion of the duodenum showed a persistent narrowing over a 4 cm segment but no ulcer crater was demonstrated. There was a sharp transition to the narrowed second portion of the duodenum from distensible bowel proximal and distal to this segment. The bulb was demonstrated to contract during the study and there was some changeability of the narrowed segment (Fig 3-5). A small bowel series revealed narrowing, irregularity of contour, and frayed mucosa in the distal two feet of ileum along with separation from the adjacent



Case 291, Fig. 4. Lateral view of stomach and duodenum with better filling again shows narrowed segment. Folds are markedly thickened. There is a sharp transition to the bulb proximally with a shouldered margin. The mucosa of the bulb is nodular and hazy.

normal bowel (Fig 6). Review of the G. I. series made six months previously showed the changes in the duodenal bulb and descending duodenum to be similar to those noted currently. No ulcer crater was identified and careful comparison of many films demonstrated some evidence of changeability of the involved descending duodenum (Fig 7). The abnormality of the duodenum was interpreted as inflammatory in origin and in view of the characteristic findings in the terminal ileum, the diagnosis of granulomatous duodenitis and ileitis was advanced.

DISCUSSION

Regional enteritis involving duodenum is not rare. Numerous case reports and reviews have appeared in recent literature (1-4). Nevertheless, relatively few of the cases have been associated with typical changes in the more distal small intestine. In the absence of such changes, even when biopsy reveals granulomas histologically, some doubt can be raised as to whether or not we are dealing with the same pathological entity which characteristically involves



Case 291, Fig. 5. Lateral view of stomach and duodenum shows that duodenal bulb does contract, albeit in asymmetric fashion. This excludes rigid encasement of the bulb by neoplasm.

the more distal small bowel. Therefore, it is worthwhile to note this case in which the characteristic changes of granulomatous ileitis co-exist with the marked inflammatory changes in the duodenum.

In analyzing the roentgen features in this case, it is of primary import to differentiate between inflammatory and neoplastic changes in the duodenum. The persistent narrowed segment with sharp transition to distensible bowel along with an absence of the normal mucosal pattern simulates neoplastic constriction with shouldered margins. Secondary involvement of the duodenum by an adjacent pancreatic neoplasm should come first to mind but the rare primary carcinoma of the duodenum should also be considered. Annular pancreas, possibly with pancreatitis, should be mentioned. However, comparison of numerous films revealed some slight changeability to the narrowed segment, contrary to what one would expect with rigid neoplastic encasement or mass. The absence of obstruction suggests that spasm plays a role in producing the narrowed segment. The duodenal bulb itself does contract although the folds are thickened and nodular. All of the features should suggest inflammatory in-



Case 291, Fig. 6. Three-hour film from small bowel study again reveals typical changes of granulomatous ileitis. The involved loops have changed their orientation in comparison to that seen on the barium enema study.

involvement of the first and second portions of the duodenum. A simple benign post-bulbar ulceration should also be considered. This is difficult to exclude entirely even in the absence of a demonstrable ulcer crater; however, it becomes very much more unlikely in view of the numerous well filled views of the duodenum without the demonstration of a crater, plus the absence of change in comparison with the study made six months previously. Ultimately, however, the typical changes in the distal ileum establish the diagnosis of granulomatous disease.

—Harvey M. Peck

Case Report: REGIONAL ENTERITIS OF DUODENUM AND ILEUM.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Seymour D. Berkowitz, Good Samaritan Hospital, Suffern, New York.



Case 291, Fig. 7. Lateral view of stomach and duodenum from a study performed six months previously shows narrowing of descending duodenum with sharp transition to distensible bowel. No ulcer crater is identified. The appearance is similar to current study.

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CASE NO. 292

A 77 year old man was admitted to the hospital following an episode of tarry stools. One year prior to admission the patient experienced colicky upper abdominal pain. G. I. series was performed which revealed a large filling defect occupying the first and second portions of the duodenum (Fig 1, 2). The mass was smoothly outlined and an ulceration was not identified. There was no ob-



Case 292, Fig. 1. Posteroanterior view of stomach and duodenum shows large, round, smoothly outlined filling defect in duodenal bulb. The mass indents the barium filled bulb on lateral aspect of the base. The distal antrum fails to fill well. The folds here are distorted. A thin linear lucency traverses distal antrum and leads to the mass. These features suggest invagination of the gastric wall behind the tumor.

struction. The patient was known to have numerous subcutaneous masses throughout his body; one of these had previously been excised and the histology revealed a typical lipoma. Because of this clinical history, the possibility of a submucosal duodenal lipoma was considered. Three months later, when the patient was asymptomatic, a repeat G. I. series now revealed a 4 cm rounded filling defect in the antrum of the stomach. The mass presented as a sessile lesion without a stalk. The surface pattern revealed no ulceration. The duodenum was normal. Again, the roentgen features suggested a submucosal tumor (Fig. 3). It was apparent that this tumor had prolapsed or intussuscepted into the duodenum at the time of the first G. I. series and had returned



Case 292, Fig. 2. Right-anterior oblique view of stomach and duodenum shows large filling defect occupying first and second portions of duodenum. The superior margin of the mass is outlined by a thin curvilinear streak of barium. Distal antrum fails to fill out and the folds are distorted.

spontaneously to its original location. Over the next nine months the patient continued to experience intermittent colicky pain which was always of short duration and subsided spontaneously. Tarry stools appeared insidiously one day prior to admission.

G. I. series after hospital admission again revealed a large antral filling defect (Fig 4). It now measured 6 cm and was lobulated, a distinct change in comparison to the previous study. A peculiar channel of barium was seen in relation to the inferior portion of the lesion suggesting an ulceration into the mass. The remainder of the stomach and the duodenum were normal.

The patient was explored and the tumor was exposed through a gastrotomy incision. It was easily mobilized and excised along with a small portion of the



Case 292, Fig. 3. Right-anterior oblique view of stomach and duodenum shows a 4 cm smoothly outlined round mass in the gastric antrum. The lesion is sessile. An ulceration is not demonstrated. Duodenum is normal.

underlying gastric wall. The pathologist reported a benign angiofibroma with a deeply ulcerated surface.

DISCUSSION

The most common tumor to prolapse from the stomach into the duodenum is an adenomatous polyp. The diagnosis is established to best advantage by observing the mass change its location fluoroscopically, first on one side of the pylorus and then on the other. The prolapse of simple gastric folds across the pylorus into the base of the duodenal bulb is seen much more commonly, best demonstrated on compression spot radiographs. The possibility of a prolapsing or intussuscepting submucosal gastric tumor is often overlooked in the differential diagnosis. Any of the submucosal tumors, such as myoma or fibroma, must be considered. In this case, a more unusual entity, angiofibroma, was reported histologically.



Case 292, Fig. 4. Compression spot radiograph of gastric antrum reveals a 6 cm lobulated mass. A peculiar channel of barium is seen traversing lower portion of the mass. This represents a deep surface ulceration.

The first report of a roentgen diagnosis of gastroduodenal intussusception appeared in 1933 (1) and subsequent well documented case reports and reviews are noted (2, 3).

The sequence of events is apparently as follows. The oncoming gastric peristaltic wave displaces the mass distally much as a surfboard rides the crest of a breaker. In this position, the mass may be displaced across the pylorus. If submucosal or sessile originally, a pseudo-stalk may be created. With the passage of the wave, the tumor may retract back to its original location or may remain trapped on the distal side of the pyloric canal. Subsequent waves may then cause even more distal displacement with a portion of the gastric wall following, and a true intussusception thus results. The negative shadow caused by the invaginated gastric wall is essential for the roentgen diagnosis (1, 2). Figure 1 demonstrates distorted antral folds, but in addition, a thin linear lucency leads to the prolapsed mass. These features suggest invagination of the gastric wall behind the tumor. The tumor spontaneously reduced itself (Fig 3) and episodic intussusception and reduction no doubt caused the intermittent colicky pain noted clinically.

Hemorrhage, the final presenting complaint, is commonly associated with submucosal tumors. The ulceration is well demonstrated in Figure 4 and correlated well with the gross pathology.

The relationship of this patient's multiple subcutaneous lipomas and the gastric lesion is not determined.

—Harvey M. Peck

Case Report: GASTRODUDENAL INTUSSUSCEPTION DUE TO ANGIOFIBROMA OF GASTRIC ANTRUM.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Seymour E. Rosenthal. Figures 1, 2 and 3 are presented through the courtesy of Dr. Norman Simon.

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CASE NO. 293

Submitted by Sanford G. Bluestein, M.D., and Charles Zimmerman, M.D.

A 28 year old housewife was admitted with a four day history of light-headedness, dyspnea and palpitation on effort. The patient had been taking aspirin in moderate dosage for the past week.

Past history revealed that the patient had had several previous episodes of massive gastrointestinal bleeding as evidenced by tarry stools and anemia. The first such episode occurred in 1956. The diagnosis was duodenal ulcer and the patient was hospitalized. Similar episodes occurred in 1957, 1958 and 1962. In March of 1962 a G. I. series was said to reveal a duodenal ulcer. Patient had been well since 1962 with no pain, tarry stools or G. I. complaints.

Physical examination on admission revealed a well developed extremely pale white female in no acute distress. Examination was entirely normal. Hemoglobin level was 5.5 gm/100 cc, red blood cell count 2.59 and hematocrit reading 20 per cent. Bone marrow revealed an iron deficiency anemia.

G. I. and small bowel examination revealed no intrinsic abnormality in the esophagus, stomach or duodenal bulb. There was no evidence of a duodenal ulcer. In the distal ileum there was an abnormal loop of bowel in which there appeared to be several nodular filling defects representing either a mucosal or submucosal tumor (Fig 1, 2).

The patient was explored. A vascular tumor was found in the distal ileum confined to a short segment of bowel. This was resected without incident. The pathologist reported a cavernous hemangioma involving all layers of the bowel



Case 293, Fig. 1. Posteroanterior abdominal film from small bowel series reveals a loop of distal ileum which has numerous nodular indentations along its inferior contour (arrows). There is no obstruction.

wall and extending into the mucosa. The tumor measured 5 x 3 cm and had a prominent central ulceration. There was no malignancy.

DISCUSSION

Hemangiomas of the intestine usually originate in the submucosa and invade the muscle layer. The serosa over the tumor remains intact but the mucosa itself may become ulcerated resulting in the clinical finding of blood in the stools or severe hemorrhage.

Most commonly, hemangiomas occur as (1) multiple phlebectasias or pinpoint varicosities, (2) cavernous hemangioma, (3) simple circumscribed hemangioma, or (4) hemangiomatosis. There is no difference in sex incidence and cases have been reported from age 2 to 80. These tumors are frequently



Case 293, Fig. 2. Magnified spot-radiograph of the lesion demonstrates the multiple nodules exquisitely (arrows). The mucosa over the nodules is smooth and the angle between nodule and the wall is obtuse, signs of a submucosal location. The opposite contour is intact. No calcifications are seen in soft tissues.

multiple and involve not only the intestine but also other abdominal organs and very frequently coexist with hemangiomatosis of the skin.

Clinically, these cases present with dyspepsia, recurrent abdominal pain, iron deficiency anemia, with and without massive hemorrhage and with recurrent melena.

Radiologically, numerous calcifications may be seen in the mesentery with irregular filling of intestinal loops, stenosis, dilatation and hazel nut type filling defects. If circumferential they may cause partial obstruction. The calcifications may be seen on plain film study of the abdomen and represent phleboliths in the lesion. None were present in this case.

The roentgen analysis in this case begins with the recognition of a lesion composed of multiple seemingly independent nodules. Multiple nodules implies tumor and there are no associated signs to suggest inflammation. The configuration of the nodules indicates a submucosal location. These features plus the history of repeated bleeding episodes should lead to the correct diagnosis.

—Harvey M. Peck

Case Report: CAVERNOUS HEMANGIOMA OF ILEUM.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. S. Jaslow and P. Shapiro, Barnert Memorial Hospital, Paterson, N. J.

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CASE NO. 294

An 85 year old man underwent evaluation for persistent hypochromic anemia with intermittently guaiac positive stool. There was no abdominal pain, change in bowel habit, gross rectal bleeding, or other gastrointestinal complaint. General physical examination was within normal limits.



Case 294, Fig. 1. Posteroanterior abdominal radiograph from barium enema study shows 3 cm narrowed segment in the mid-descending colon. A few tiny diverticula are seen in the proximal sigmoid without roentgen indication of diverticulitis here. Remainder of colon is normal. There is no obstruction.



Case 294, Fig. 2. Compression spot radiograph of the lesion in the mid-descending colon reveals lobulated shouldered margins proximally and distally. Linear strands of barium traverse the lesion longitudinally and there is no normal mucosa in this segment. The appearance is reminiscent of a channel through a neoplasm which encircles the bowel. There is no obstruction, however.

A barium enema was performed. Barium flowed freely from rectum to cecum. An obvious narrowing in the mid-descending colon was observed fluoroscopically. Numerous spot films were obtained as well as conventional radiographs (Fig 1, 2). An air study was also performed. All views demonstrated a persistently narrowed segment without normal mucosa and with shouldered margins proximally and distally. There was no obstruction. The appearance was typical of an annular constricting carcinoma.

The patient was explored. A firm narrow segment in the mid-descending colon

was palpated, and a local resection was performed. The pathologist reported a short segment of diverticulitis with marked thickening of the wall of the bowel due to inflammatory reaction. The mucosa was effaced but not ulcerated. A single diverticulum in the center of the specimen was obstructed and was apparently the origin of the inflammatory process. There was no malignancy.

DISCUSSION

This case is presented in order to emphasize the difficulty which can arise in differentiating between diverticulitis and carcinoma. It is difficult to avoid arriving at a diagnosis of neoplasm on the basis of the examination as presented. There was no definite changeability on the barium films as well as on the air contrast films. The lesion was short, circumferential, and had shouldered margins. Normal mucosa was not seen. There was no surrounding spasm or irritability and no diverticula were noted in the involved segment. There was no obstruction; perhaps this one finding should give pause in the face of an annular lesion and suggest that an element of spasm is present.

Many different inflammatory colonic lesions can simulate neoplasm. In addition to nonspecific diverticulitis, these include specific inflammatory lesions (1), granulomatous colitis, vascular lesions, infarcted appendix epiploica, foreign body perforation, appendicitis with cecal deformity, and many more. The radiologist is conditioned to think of diverticulitis in lesions of the sigmoid, but the possibility of diverticulitis elsewhere in the colon is often not weighted sufficiently in the differential diagnosis.

—Harvey M. Peck

Case Report: DIVERTICULITIS OF DESCENDING COLON SIMULATING CARCINOMA.

ACKNOWLEDGMENT

This case is presented courtesy of Dr. Isadore Gerber, Dr. Arthur H. Aufses, Jr., and Dr. Arthur W. Ludwig.

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Emergency Liver Resection for Primary Carcinoma

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Massive resection of the liver has become an acceptable elective operation, as the result of clearer delineation of the anatomy of the liver (and therefore more precise control of hemorrhage) and understanding of the nature and management of the metabolic changes following removal of a large part of the liver.

Complete preoperative evaluation of the patient including history, liver function tests, liver scanning and detailed knowledge of the extent of the disease is necessary before deciding on the advisability and extent of the proposed resection. The operation should be planned so that adjunctive measures such as hypothermia may be included. This desirable situation is precluded in emergency situations such as severe trauma to the liver in which hemorrhage is the prime indication for exploration and resection.

A case is reported in which successful right hepatic lobectomy, removing 80% of the liver, was performed as an emergency procedure for primary hepatic cell carcinoma.

Case Report

A twenty-five-year-old Negro woman was admitted with a ten hour history of epigastric pain increasing in intensity without radiation and accompanied by vomiting. She was febrile (100.4 F) and on physical examination displayed exquisite tenderness in the epigastrium overlying an area occupied by a smooth-walled tender mass which moved on respiration and blended laterally into the anterior edge of the liver along the right costal margin. The white blood count was 10,000/cu mm with many immature forms; Hemoglobin value was 11.3; Serum amylase and electrolytes were normal. A differential diagnosis of either pancreatic cyst or liver tumor with hemorrhage was made preoperatively and the serious abdominal signs indicated the need for surgical intervention; this was performed as an emergency the first evening of admission.

At operation, a melon-sized (12 cm) solid and vascular tumor was found presenting beneath the gastrohepatic ligament in the region of the lesser sac (Fig 1). On examination this was found to be a tumor arising from the under surface of the right side of the liver. Approximately two-thirds of the tumor extended outside the liver and it was this part that was pushing to the left beneath the porta hepatis to present behind the gastrohepatic ligament. A frozen section indicated hepatocellular carcinoma and a right total lobectomy was performed.

Immediately postoperatively, the patient received vigorous replacement of serum albumin and plasma as well as 10% glucose and fructose infusions to prevent the serious complications of hypoproteinemia and hypoglycemia that attend major hepatic resection. Despite the administration of 50 grams of albumin daily the serum albumin level showed a slight decrease but with continued albumin infusion it was kept within an acceptable range (Fig 2). The need for hypertonic glucose diminished after three days

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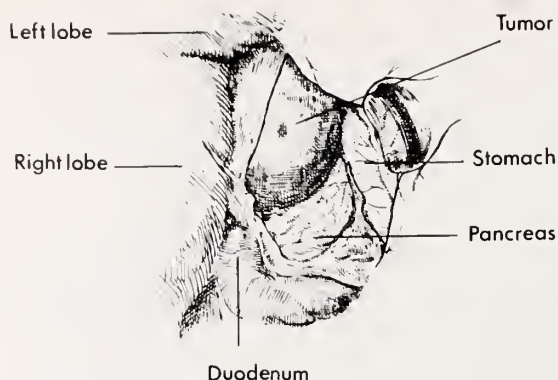


FIG. 1. Operative Findings. Tumor is largely extracapsular arising from undersurface of right lobe and has herniated beneath porta hepatis to present behind lesser omentum.

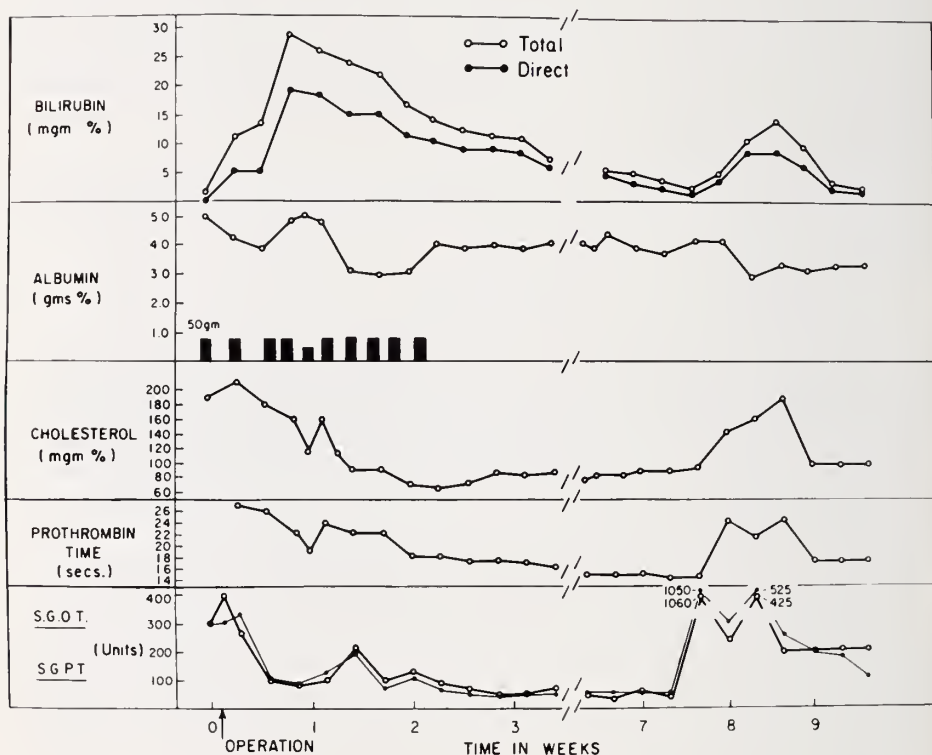


FIG. 2.

and the patient was soon able to take oral feedings in satisfactory quantities. Prothrombin clotting time was abnormally prolonged for several weeks despite Vitamin K administration. During the first postoperative week there was some abnormal vaginal bleeding but the entire coagulation profile except for the prothrombin time was normal. Serum bilirubin increased rapidly to a level of 28/18 and then gradually returned in slow stages toward normal. Serum cholesterol levels fell and stayed low for several weeks.

The serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic

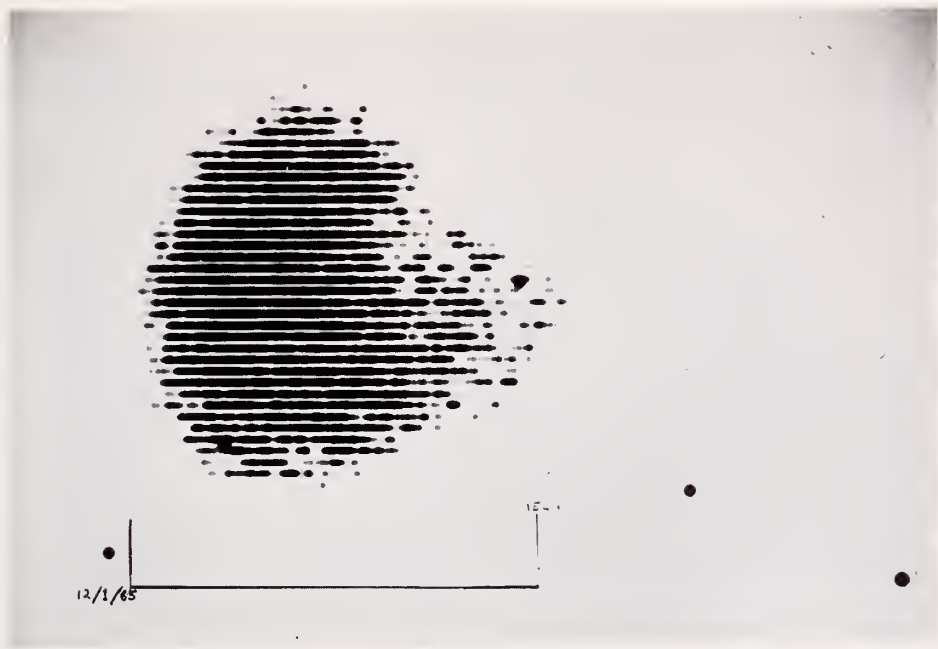


Fig. 3A. First scan three weeks after operation. Functioning liver tissue seen in area of right lobe.

transaminase (SGPT) rose initially, then fell to normal levels and stayed normal for several weeks. By the eighth postoperative week all liver function tests were within normal limits. The patient was eating well and was ready to go home except for some persistent purulent drainage from the site of a sump tube which had been placed in the right subphrenic space previously occupied by the right lobe of the liver. This slowly dried up and closed. By the eighth postoperative week, the patient complained of lethargy, weakness and anorexia. Within a few days it was obvious that she again had jaundice. Investigation showed an elevation in serum bilirubin and prolongation of prothrombin time as well as conspicuous elevation in SGOT and SGPT. The diagnosis of serum hepatitis was made and she was treated expectantly. Within two to three weeks there was obvious improvement with the return of liver function tests toward normal levels; a persisting mild mental depression was treated with Elavil® and psychotherapy. She was discharged in the twelfth postoperative week with normal liver function and has now been followed in the out-patient clinic one year after the operation; she appears essentially well. Liver scans using radioactive gold have shown regeneration of the liver to normal size (Fig 3 A, B, C) and she is currently asymptomatic, gaining weight (15 lb) and resuming housework chores. A subsequent episode of purulent discharge from below the right costal margin was treated by drainage, removal of two silk sutures and packing. No clinical evidence of recurrence is apparent 15 months later.

Liver cell carcinoma has well defined geographic and racial distributions. It is a rare disease in the United States and Europe, and in Britain accounts for only one percent of all malignant disease (1). It is the most common malignant tumor in Javanese males and one of the most common in Japan. In Bantu Negroes it accounts for 50% and in young Bantu gold miners 87% of all malignant disease (2). In Chinese, both in China and Malaya, it accounts for 14% of cancers.

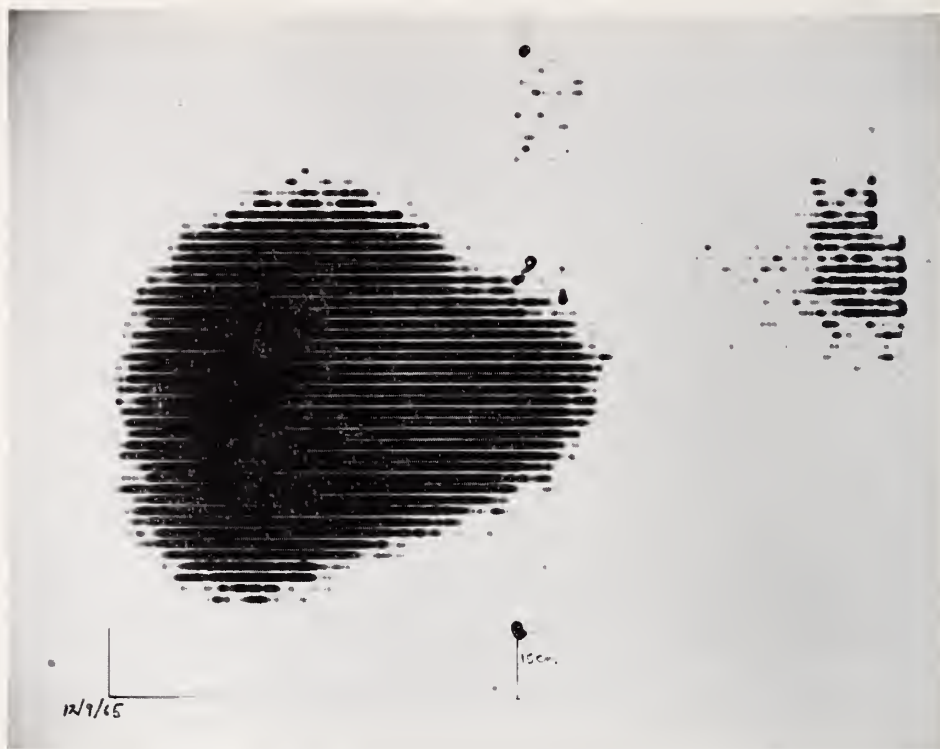


FIG. 3B. Nine days later showing progression of regeneration.

There is an overwhelming association of the disease with cirrhosis of the liver, usually of Laënnec's type, this association occurring in 60 to 90% of cases. In those countries with high incidence of carcinoma of the liver it is seen in 16 to 51% of males with cirrhosis. This cirrhosis appears to be related to dietary deficiencies or toxic food factors rather than to alcoholism (3, 6).

In a series of 48,900 consecutive autopsies in Los Angeles, Edmondson (4) found the overall incidence of carcinoma of the liver to be 0.01%. Cirrhosis was found in 2.6% while 4.4% of the cirrhotics had liver carcinoma. Breakdown of the figures for cirrhotics on an ethnic basis showed that whites had 3.4% incidence of carcinoma of the liver, Negroes 14.5% and Mongolians 33.3% although this last figure may not be statistically significant because of relatively small numbers.

While carcinoma in association with cirrhosis had strong preponderance among males, carcinoma in the absence of cirrhosis was seen most commonly in females. Liver carcinoma in infants and children usually occurs in non-cirrhotic males.

Etiology

Apart from cirrhosis of the liver other factors have been associated with liver cell carcinoma. These include liver calculi, ionizing irradiation, parasitic infestation, thorotrast injections, viral hepatitis, hemachromatosis of endogenous type

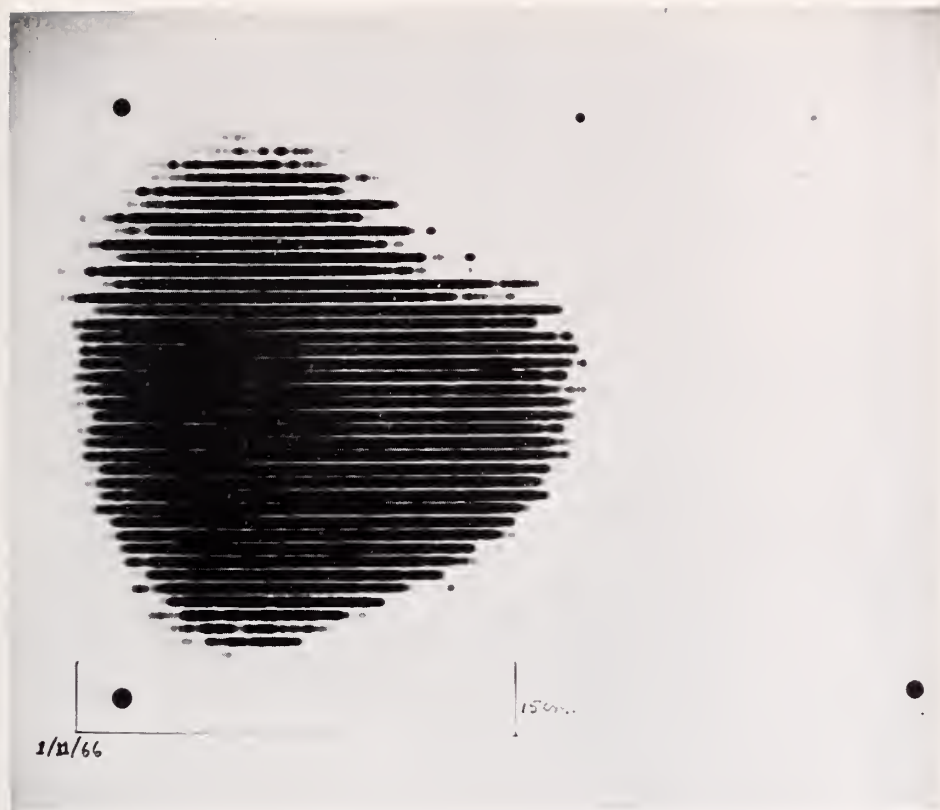


FIG. 3C. One month later showing progression of regeneration.

and postnecrotic cirrhosis (6). Primary liver carcinoma is twice as common in diabetics than in the general population. No specific factors have been implicated in the primary carcinoma of infants and children but since occurrence of the disease in this age group is commonest in areas where the disease is most prevalent it may be the result of the effect of malnutrition on the liver.

Clinical Features

The most frequent complaints include weakness, right upper quadrant pain, weight loss, jaundice, vomiting, abdominal swelling and gastrointestinal hemorrhage. There may be swelling of the legs if the inferior vena cava is invaded. Physical examination may reveal, in addition to the stigmata of cirrhosis, an enlarged tender liver with a palpable tumor, low fever, ascites and anemia. The spleen may also be palpably enlarged. Visible metastases are rare. Rarely a venous hum may be heard. Radiographs may show a high or fixed right diaphragm. With extensive liver involvement there may be recurrent attacks of hypoglycemia due to excess glycogen storage, or, rarely, hyperthrombocytopenia.

The patient may present as an acute abdominal emergency, as this patient did, due to hemorrhage either into the tumor or from its surface into the general

peritoneal cavity. A small tumor on the upper surface of the liver may give rise to a huge subphrenic hematoma. Hemobilia may occur if there is bleeding into the biliary passages and colic may occur from the passage of clots.

The diagnosis may be made only at operation but the suspicion may be confirmed by liver scanning with I^{131} tagged Rose Bengal or radioactive gold Au^{198} , by pneumoperitoneal radiography, splenoportography, transhepatic arteriography, celiac angiography or peritoneoscopy. Biopsy, either open or percutaneously with a needle, will confirm the diagnosis while an indication of the extent of liver damage may be obtained by the usual tests of liver function.

Prognosis

In cirrhotics with carcinoma the life expectancy averages three to four months from onset while in non-cirrhotics it may be measured in years.

Treatment

Resection of circumscribed or massive carcinomata in non-cirrhotics offers the only hope of cure. The multinodular tumor in cirrhotics is not amenable to curative treatment.

Pathology

Liver cell carcinoma is a malignant tumor derived from hepatic parenchymal cells. Synonymous and related terms include carcinoma simplex, carcinoma solidum, hepatic cell carcinoma, hepatocellular carcinoma, hepatoma, malignant hepatoma and trabecular carcinoma.

Most of these tumors arise in livers showing advanced Laënnec's cirrhosis, only a few appear in otherwise normal livers. They may be classified as massive, nodular or diffuse or rarely may be pedunculated. The right lobe is far more frequently involved than the left and may be largely replaced by tumor. The massive variety may have smaller secondary nodules in the surrounding liver. In the nodule type the liver tends to be completely replaced by tumor but often one nodule may be identified as the primary tumor by necrosis and hemorrhage within it. The tumor may grow in an expansile manner leading to pseudoencapsulation.

Typically the portal radicles are invaded and distended by tumor thrombi. Less frequently the hepatic veins are involved, a few extending into the inferior vena cava or as far as the right atrium of the heart.

Microscopically the appearance is greatly variable ranging from adult cell types containing bile to highly anaplastic tumors. Areas of adenocarcinoma may be present and variants include spindle cell tumors, giant cell carcinoma with diffuse stroma and tumors containing both liver cell and bile duct carcinoma. Important criteria in making the diagnosis include the similarity of tumor cells to hepatic cord cells, the trabecular nature of the growth, intravascular extension of the tumor and the formation of canaliculi on acini (5).

Metastases

Liver cell carcinoma may spread via the hepatic veins to lungs, pleura, bone, adrenals, brain and myocardium; via the portal vein to pancreas, spleen, verte-

brae through vertebral veins, falciform ligament and umbilical area; via the peritoneum to the pelvic cavity; via lymphatics to periportal, peripancreatic, retroperitoneal, periaortic and tracheobronchial lymph nodes. Direct local spread may involve structures immediately adjacent to the liver.

Indications for Hepatic Lobectomy are as follows:

Benign:

Tumors.....Massive hemangioma, hamartoma, embryoma.

Cysts.....Simple and echinococcal.

Abscesses.....Large single or multiple.

Trauma.....Multiple fractures or gunshot wounds.

Malignant: Primary liver carcinoma, cholangiocarcinoma, sarcoma.

Metastatic.....Gallbladder; some slow growing tumors such as colon malignant carcinoid.

Segmental resection for benign tumors should result in an excellent prognosis (7); it may sometimes be the most expedient method of treating cysts and abscesses (8). Severe traumatic damage is being treated with increasing frequency and more satisfactorily by resection than by oversewing and packing; indeed this may be the only way to control massive bleeding from a damaged liver.

While most malignant tumors of the liver are not seen at a stage sufficiently early for cure by resection an occasional case may be encountered in which the tumor is localized and resectable (6-10). Primary cholangiocarcinomas are usually multiple and widespread throughout the liver, making resection impossible, while primary hepatic cell carcinoma grows rapidly making it unlikely that it will be diagnosed early enough to give a favourable outcome. However, incidents in the course of the disease which bring the tumor to the attention of the surgeon in an early phase may allow successful exploration. These include hemorrhage into the tumor, as in the case reported here, or from the tumor surface into the general peritoneal cavity.

The indications for resection of a metastatic tumor in the liver are less clear-cut. In the case of carcinoma of the gallbladder with limited liver invasion, or a colonic carcinoma which is relatively slow growing, a solitary metastasis may be resected with success (7, 8). It may be debated that the lesion found in the liver is not a solitary metastasis but that there is more extensive disease which is not obvious at the time of exploration. Wilson has reported dramatic palliation of the symptoms of malignant carcinoid by massive liver resection (12).

Anatomy

The classical anatomical division of the liver into right and left lobes by the falciform ligament does not take into consideration the blood supply of the liver. Studies of the blood supply and biliary drainage (13-18) show the liver to have a segmental structure. The hepatic artery, portal vein and hepatic ducts

all have similar intrahepatic courses with little variation so that a definitive and surgically useful description can be based upon them.

The true right and left lobes of the liver are demarcated by a lobar fissure which extends from the fossa of the gallbladder to the fossa of the inferior vena cava. The left lobe is subdivided into medial and lateral segments by the falciform ligament so that the lateral segment corresponds to the entire left lobe of the earlier descriptions while the medial lobe corresponds to the quadrate lobe. The left lobe accounts for just under 20% of the liver weight.

The right lobe is subdivided into anterior and posterior segments each divided further into superior and inferior areas. The only area with a dual blood supply is the caudate lobe which is supplied from both left and right sides.

The hepatic veins do not have a similar segmental distribution but lie in the intersegmental planes at right angles to the afferent vessels. There are usually three hepatic venous trunks, right, middle and left (Fig. 4). The right drains the posterior segment and the superior area of the anterior segment of the right lobe. The middle drains the inferior area of the medial segment of the left lobe and the inferior area of the right anterior segment. The left drains the lateral segment and the superior area of the medial segment of the left lobe. There is some variation in the way in which these veins enter the inferior vena cava. The right enters on the right of the vena cava; the other two veins usually enter separately on the left but may combine as a common trunk. There may be additional small branches which are inconstant.

Operative Technique

The liver may be explored through an upper midline incision and the diagnosis confirmed if necessary by biopsy. If the left lobe appears to be free of tumor the incision is then extended into the right chest through the seventh or eighth costal cartilage and intercostal space. The diaphragm is incised from the divided costal cartilage to the caval foramen and the hepatophrenic ligaments divided. The liver is then dislocated upwards, the structures in the free edge of the lesser omentum identified and traced upwards into the porta hepatis. The branches of the portal vein, hepatic duct and hepatic artery going to the right lobe are ligated and divided. This results in pallor of the right lobe so that its left limit can be defined easily (Fig 5).

The hepatic veins are approached next. The right lobe is pulled downwards and to the left and the right hepatic vein identified as it enters the cava. It is divided between ligatures. The middle and left hepatic veins must be examined carefully to ensure that the venous drainage of the left lobe will not be impaired.

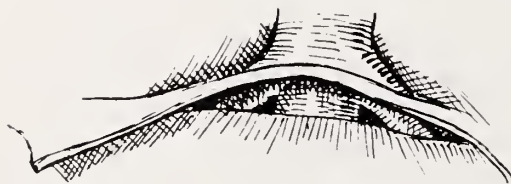
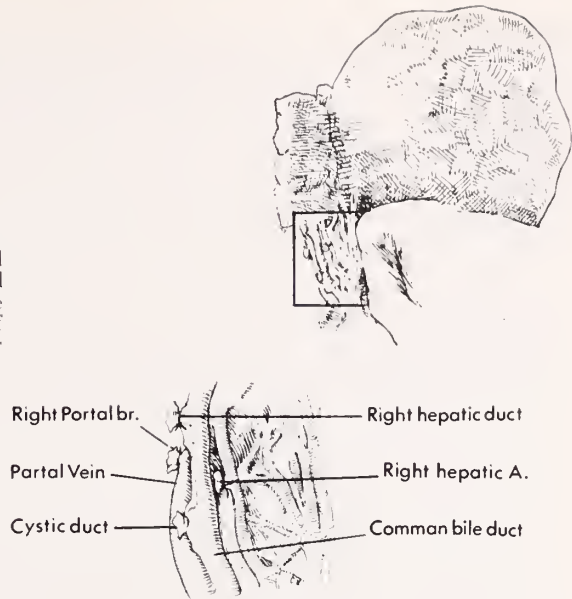


FIG. 4. Anatomy of Hepatic Veins. Three main hepatic veins is most common arrangement. Note short length of major veins outside of liver capsule.

FIG. 5. *Top*, Configuration at end of procedure. All of right lobe and 4/5 of medial segment of left lobe removed. *Bottom*, Anatomy of structures in porta hepatis after dissection.



If necessary, a conjoined trunk may be traced for a short distance into the liver to define the separate channels. The right lobe is then swung further over to the left to expose the anterior surface of the cava and any accessory veins from the right lobe are ligated and divided. The hepatic veins must be approached with caution as they are fragile and any damage to them might result in hemorrhage which is very difficult to control (14, 15).

The liver may now be divided through a line just to the right of the falciform ligament to ensure that no liver is left behind which has been deprived of its blood supply.

While a guillotine amputation of the lobe may be the fastest method of removal in the case of severe hemorrhage, the use of electrodiathermy is more hemostatic than a scalpel blade; the method of blunt division with the point of a hemostat gives the least blood loss. The instrument divides soft liver tissue allowing taut strands of vessels and ducts to be identified, ligated and divided separately.

The diaphragm is sutured and closure effected in the usual manner leaving drains in the right pleural cavity and in the subdiaphragmatic liver bed. Placing a T-tube in the common duct is recommended by some authors.

Anesthetic Considerations. The most important considerations are maintenance of adequate blood volume and oxygenation during the procedure. If total hepatic inflow is expected to be interrupted for longer than 10 to 15 minutes, hypothermia has been advised. There is no contraindication to any specific anesthetic agent.

Metabolic function. The actual extent of metabolic derangements following major liver resection depends upon the amount of liver substance remaining

and its role in metabolism prior to operation. If the resected portion is badly diseased or nonfunctioning the segment remaining after surgery may already have taken over an increased functional role, thus diminishing the postoperative derangements often expected. Consideration of derangements and therapeutic requirements may be easily classified into subdivisions represented by the common liver function tests.

Pigment metabolism. The most common finding after partial hepatic lobectomy is an abrupt rise in serum bilirubin followed by a gradual but progressive return to normal levels. The degree of hyperbilirubinemia is often dependent upon the amount of bank blood transfused during surgery as well as metabolic capability of the remaining liver.

Protein. Albumin, which is metabolized at a rapid rate, will fall rapidly in the postoperative period and must be replaced intravenously in order to prevent hypoalbuminemia with loss of colloid osmotic pressure, anasarca, and increased interstitial fluid with pulmonary edema and death. Intravenous albumin, 50 grams per day for 6 to 10 days, has been found satisfactory to maintain a normal serum level, but daily determinations of serum albumin are essential to verify the efficacy of the rate of infusion.

Carbohydrate metabolism. Because of the loss of the liver glycogen reserve system there is an abrupt fall postoperatively to severe hypoglycemic levels. The patient presented had a blood glucose of 52 mg/100 cc in the immediate postoperative period. Fructose is better than glucose for replacement of circulating blood sugars because it is more rapidly and effectively converted to liver glycogen and appears superior to glucose in its nitrogen sparing effect. After approximately 48 hours, replacement of circulating glucose is no longer essential and indeed a mild hyperglycemia is often found.

Clotting factors. The prothrombin time is seriously affected and frequently remains above normal for several weeks despite daily administration of Vitamin K. Other workers report minor transient fall in fibrinogen as well as factors V and VII, which return to normal within a week. There were no such clotting derangements in our patient.

Fat. Nonesterified fatty acids (NEFA) are the precursors of serum triglycerides and are mobilized from adipose tissue in the normal subject and processed in the liver. Thus, in a patient in whom part of the liver has been removed, the NEFA will abruptly fall until gradual return of both of these levels toward normal in approximately 6 to 9 days. No treatment is necessary. Serum cholesterol, a sensitive index of fat metabolism, falls abruptly to very low levels and will rise very slowly toward normal over the next 4 to 6 weeks, as in this patient.

Ammonia intoxication is not a problem provided there is no underlying liver insufficiency. The patient can eat a normal diet soon after operation without fear of ammonia intoxication.

Management. In patients with known preexisting liver disease careful control of prothrombin time and serum albumin levels is important. Inability to

correct these indicates a poor prognosis and should contraindicate elective major liver excision. Premedication for anesthesia should be minimal as most of the premedication drugs used are metabolized in the liver. A high calorie, high carbohydrate diet should be employed prior to elective surgery and 10% fructose should be used intravenously during and after surgery. Postoperatively administration of serum albumin and Vitamin K with attention to clotting function is important. For any deranged clotting mechanism, fresh blood or specific plasma fractions should be administered as indicated.

Regeneration of Liver

After massive resection regeneration of the liver occurs from the remaining tissue in a remarkably short time. In the rat, normal liver bulk is reached in 12 to 18 days. In the dog, it takes about eight weeks. In man, after 80% resection, most liver function tests return to normal levels in three weeks; the regenerated area assuming a rounded sperical shape which may appear as a mass in the epigastrium.

From clinical experience with postoperative scanning in a limited number of patients who have had a second laparotomy, liver regeneration has been noted to occur in approximately 3 to 6 months following major resection (19, 20). In this case, within two months, there was evidence of complete regeneration of liver size (Fig 4). It should be noted that this is true hyperplasia with actual budding of a lobular system and with normal fat, water, and nitrogen content in the cells. Normal biochemical status is expected within 2 to 3 weeks after operation but occasionally takes longer. In the patient reported here, with acute presentation and without destruction of the right lobe, it is unlikely that the remaining liver had begun any adaptation and this is probably the reason why the return towards normal metabolic function was prolonged.

Summary

A clear understanding of the anatomy of blood supply and drainage of the liver and the physiologic derangements which follow surgical procedures on the liver have made major hepatic resections an appropriate procedure in surgical therapy.

A case is reported of a malignant tumor of the liver, presenting as a surgical emergency, for which right hepatic lobectomy was successfully performed.

A brief review of the pathology and management of carcinoma of the liver is presented.

Anatomic features and the metabolic response to a major hepatic resection are discussed.

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Mediastinoscopy: Experiences with Fifty Cases

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INTRODUCTION

In 1959, Carlens (1) described a method of inspection and biopsy of the superior mediastinum through a cervical incision. This procedure, called "mediastinoscopy," is based upon knowledge of the anatomical continuity of cervico-mediastinal areolar tissue planes, particularly the avascular plane of the pretracheal fascia. Examination of this diagnostically fertile area is aided by the insertion of a "mediastinoscope"—a cylindrical lighted speculum—into a tunnel in the pretracheal fascial plane which has been developed by digital dissection. Mediastinal lymph nodes are readily available for biopsy and yield valuable information since they so frequently reflect intrathoracic disease of almost every variety. Tumors of the superior mediastinum may be sampled and occasionally cystic lesions can actually be removed by this operation.

While the origins of "cervical mediastinoscopy" can be found in the valuable scalene fat pad biopsy of Daniels (2), and its modifications by Harken (3), Radner (4), Lui (5) and many others, it remained for Carlens to formalize direct transcervical mediastinal exploration. Excellent monographs by Palva (6) and Jepsen (7) are recommended for detailed review of extensive experiences with the Carlens procedure.

Mediastinoscopy enjoyed prompt acceptance and widespread use in Europe and Canada, but only relatively recently have its advantages been exploited in the United States.

Since October 1965, fifty mediastinoscopies have been performed at The Mount Sinai Hospital and form the basis for this report.

TECHNIQUE

Mediastinoscopy is best performed under general endotracheal anesthesia. In rare special instances, local anesthesia may be employed.

The patient is positioned supine, the back elevated by several folded sheets under the scapulae, the neck hyperextended and the head rotated to one side. Appropriate draping allows the anesthetist to work alongside the patient while the surgeon and his assistant stand at the head and other side.

A 3 to 4 cm transverse incision is made in the suprasternal notch about 2 cm above the manubrium similar to but slightly lower than that used for tracheostomy. With the wound spread vertically the median raphe is split and the strap muscles are retracted to expose the anterior surface of the trachea inferior to the thyroid isthmus (Fig 1a). The loose areolar avascular plane of the pretracheal fascia is entered and by blunt digital dissection with the index finger, a tunnel is developed into the superior mediastinum hugging the anterior tracheal wall (Fig

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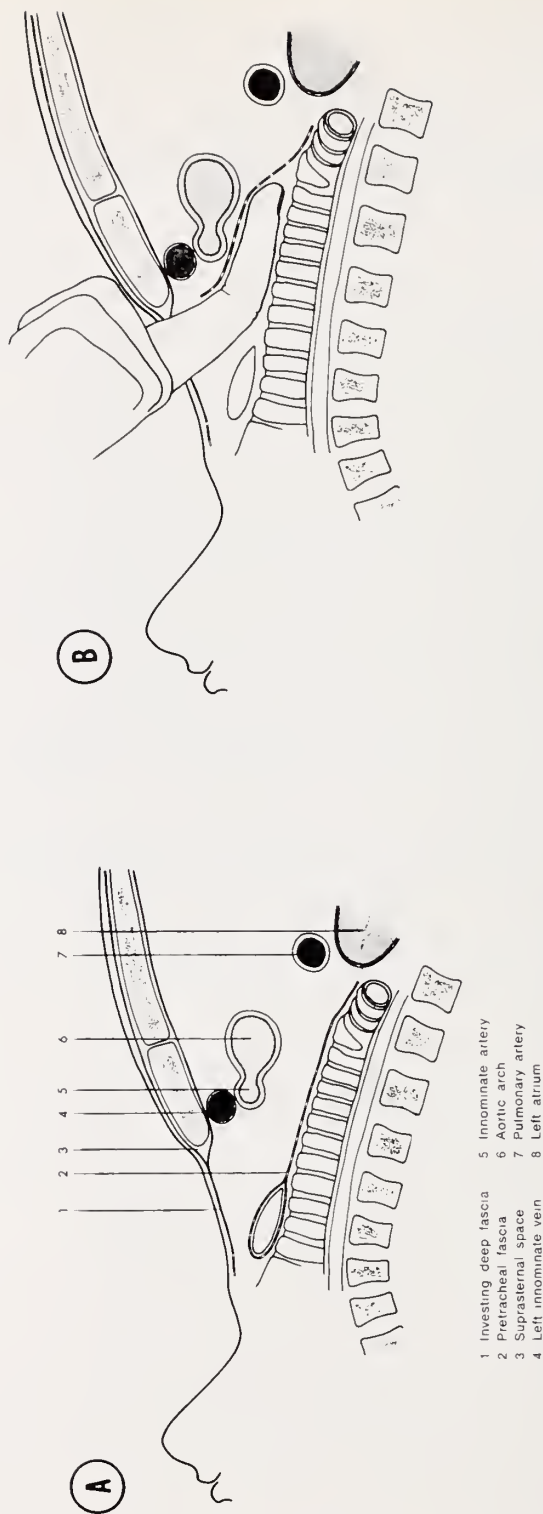


FIG. 1. Technique of Mediastinoscopy (after Jepsen, 1966, with permission of the publisher). A. Sagittal section through neck and mediastinum showing anatomical landmarks and relationships. Note "pretracheal fascia." B. Finger dissection beneath pretracheal fascia to develop pretracheal "tunnel."

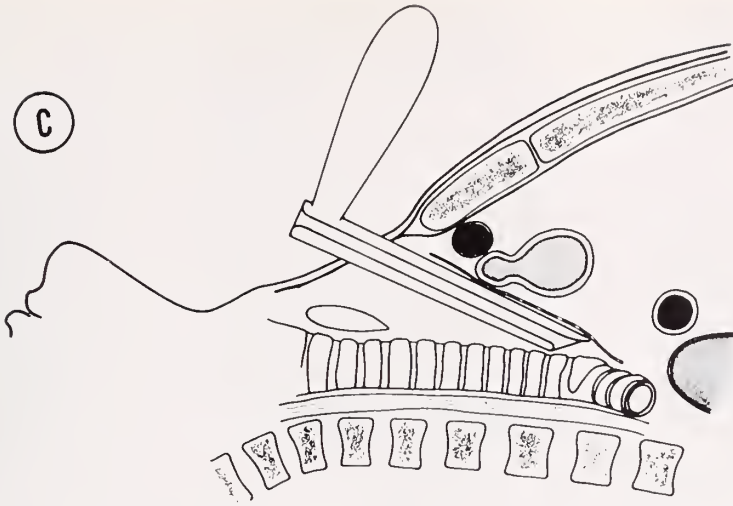


FIG. 1C. Mediastinoscope inserted into pretracheal "tunnel."

1b). The exploring dissecting finger passes posterior to the innominate artery (sometimes visible in the wound) and the aortic arch. The level of the tracheal bifurcation represented externally by Louis' angle at the level of the second costal cartilage, can be reached in most individuals. Cautiously, the tunnel is widened on either side of the trachea down to both main bronchi.

While this dissection is carried out the surgeon may palpate nodes or masses. Pathological nodes may present as large discrete succulent glands, small fibrotic nodules, hard matted masses or broken down necrotic tissue. Tumors and cysts are also palpable—the latter varying from lax to tense in consistency.

Only after a sufficiently capacious tunnel has been prepared is the mediastinoscope introduced and advanced into the mediastinum keeping the anterior tracheal wall in view (Fig 1c). It is not inserted primarily, nor forced into the mediastinum. Further dissection is carried out through the mediastinoscope with gauze strips and pledgets manipulated with long forceps and a long suction tip.

Lymph nodes are recognized by their anthracotic pigment and are best visualized in the right paratracheal area. Sometimes they are purplish-red and may resemble large vessels. It is wise to aspirate a questionable node before biopsy using a long 21 gauge needle. As dissection proceeds, both main bronchi, the azygos vein, subcarinal and peribronchial nodes and the right pulmonary artery may be seen. After a node or tumor tissue is sufficiently defined, punch biopsy or complete removal of a node can be accomplished. Ordinarily very little bleeding results and is easily controlled with gauze pressure or absorbable hemostatic gauze (Gelfoam or Surgicel). A Vim-Silverman or Menghini needle may be used to obtain tissue from a mass.

Biopsy specimens should be examined by frozen section during the operation to be sure that sufficiently diagnostic tissue has been obtained. Silver brain clips

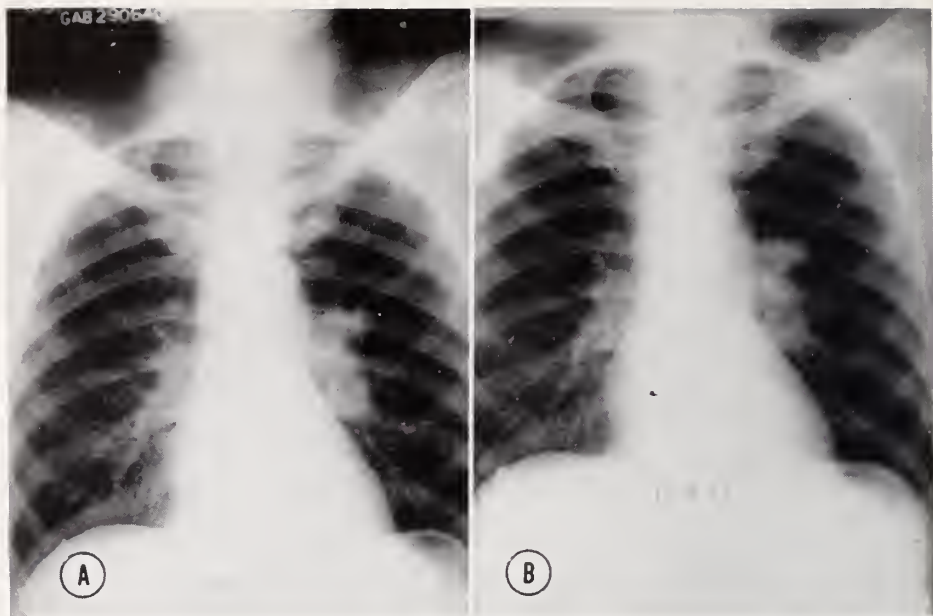


FIG. 2. Case 1. Adenocarcinoma. A. Chest x-ray film 8/31/65 shows hilar and left mediastinal adenopathy. B. Chest x-ray film 10/5/65 now shows right paratracheal node.

may be placed at the biopsy site or other special areas for subsequent radiologic identification.

If tumor tissue or nodes are encountered paratracheally relatively high in the mediastinum exposure for biopsy may be achieved with narrow ribbon-type retractors rather than by using the mediastinoscope.

At times it may be deemed advisable to precede mediastinoscopy with scalene biopsy. The typical scalene exposure is made first, and if frozen section is negative, the incision is extended medially anterior to the sternocleidomastoid muscle into the suprasternal notch and formal mediastinoscopy is carried out.

If mediastinal involvement is anterior to the aorta and substernal, dissection can be carried out here into a similarly avascular plane. Transcervical thymectomy has been reported by this method (8). This variation of mediastinal exploration has limited applicability. Direct anterior mediastinotomy is more valuable in this instance.

The wound is usually closed primarily. If drainage is desired it should be of a suction variety as the mediastinal pressure is subatmospheric. A postoperative chest x-ray film is made in the recovery room. Antibiotics need not be used routinely.

Bronchoscopy and/or esophagoscopy is easily performed at the same sitting with mediastinoscopy utilizing the same endotracheal anesthesia. Also, if circumstances are favorable, open thoracotomy and lung resection can follow the mediastinoscopy without added risk.

A setup for emergency thoracotomy and transfusion should be readily avail-

able in case of hemorrhage or other untoward complication during mediastinoscopy.

INDICATIONS AND DISCUSSION

The chief indication for mediastinoscopy is intrathoracic disease which may involve the mediastinal lymph nodes. It is appropriately employed when a specific diagnosis cannot be made by other means (i.e. bronchoscopy, sputum cytology and bacteriology, scalene biopsy, Kveim test, angiography, scanning technics, etc.) and when it is essential to determine the existence of metastatic tumor in the nodes. Lung cancer overwhelmingly heads the list which includes sarcoidosis and other granulomatous diseases, tuberculosis, lymphomas, pneumoconioses, and esophageal cancer. Other indications are mediastinal tumors and cysts where primary open thoracotomy is not deemed desirable.

In most cases there is roentgenologic evidence of superior mediastinal widening or mass, usually in the right paratracheal area. This is the most fruitful site for biopsy as the right paratracheal group of lymph nodes is the main terminus of the tracheobronchial lymphatic system. Other evidences of adenopathy include widening and blunting of the carinal angle by subcarinal glands, esophageal indentations on barium swallow, and left paratracheal enlargements. A positive diagnosis can be obtained even if the mediastinal contour is normal.

The numerical importance of lung cancer makes it worthwhile to discuss this disease in some detail. Once a specific diagnosis has been made, or strongly suspected from the chest roentgenogram and clinical picture, operability must be determined. The main local contraindication to surgery is metastatic spread to mediastinal nodes. Despite the availability of methods of radical mediastinal



FIG. 2C. Case 1. Adenocarcinoma. Mediastinoscopy in progress. Note the large gland removed from the right paratracheal area and the healed left scalene incision.

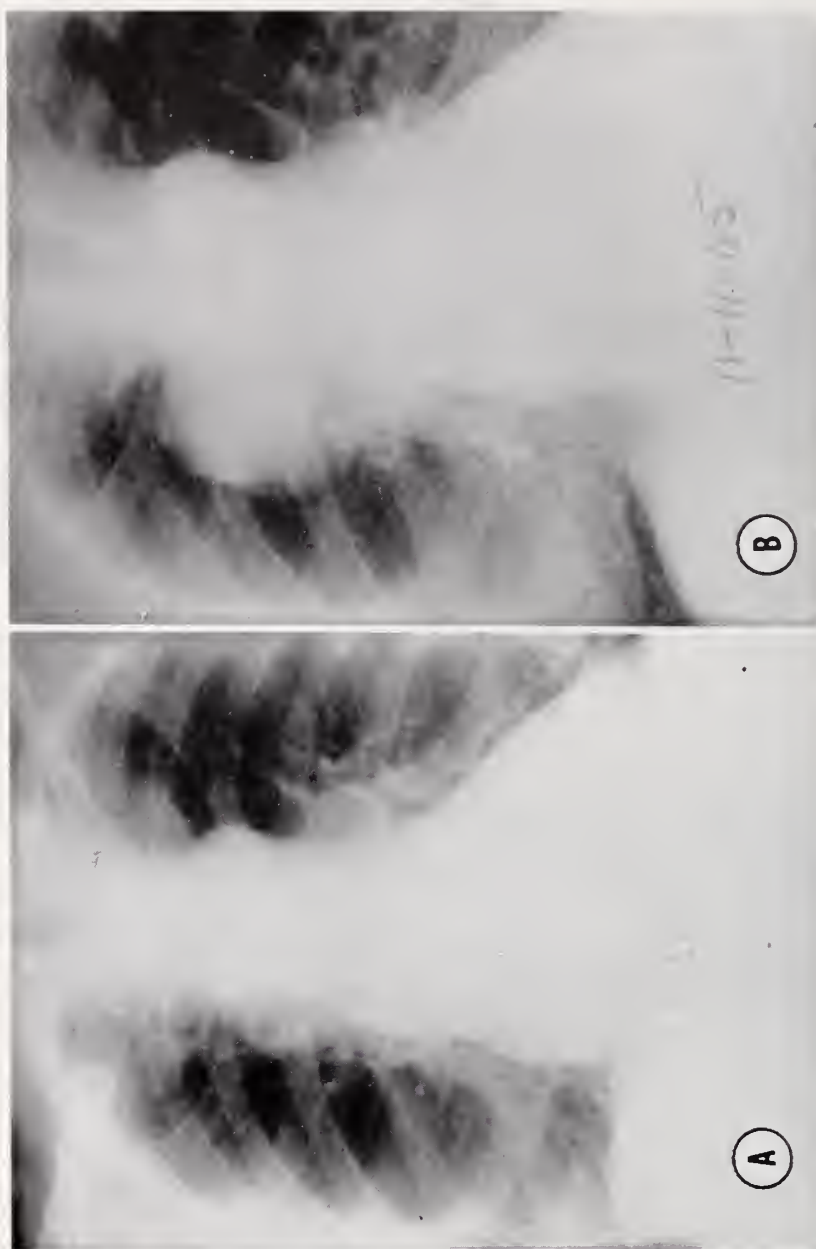


FIG. 3. Case 2. Anaplastic carcinoma. A. Chest x-ray film 11/11/65. Five years later mass is much larger. Still asymptomatic. Mediastinoscopy performed at this time. B. Chest x-ray film 6/28/60. Asymptomatic right paratracheal mass.



FIG. 4. Case 3. Hodgkin's disease. Superior vena cava syndrome. Huge anterior and middle mediastinal mass.

dissection, a large number of such cases are technically unresectable. Even when excision can be accomplished in the presence of involved mediastinal nodes, prognosis is very poor. Indeed, many surgeons regard such cases as primarily inoperable and resort to radiotherapy as a definitive or preoperative mode of treatment.

The question of preceding or accompanying mediastinoscopy with the Daniels scalene fat pad biopsy is commonly raised. In the classical sense, the Daniels procedure refers to *non*-palpable nodes. Moreover Daniels himself described digital exploration of the superior mediastinum as part of his procedure. The yield of scalene biopsy in lung cancer with *non*-palpable nodes is so low that its performance in such cases has been questioned by Leckie et al (9). The large literature on scalene biopsy is confusing because the differentiation between palpable and non-palpable nodes is often not made. Harken et al (3) very early, and subsequent comparison studies by others later, indicated that the Carlens procedure will afford positive biopsies three times as frequently as the scalene biopsy.

Another consideration is that the Daniels biopsy is unilateral (unless both sides of the neck are explored) while the Carlens operation is bilateral in scope. Furthermore, crossed metastases have been detected in about 20% of cases (Jepsen (7), Pearson (10)). At present we favor primary mediastinoscopy over preliminary scalene biopsy.

The above remarks do not detract from the value of scalene biopsy in sarcomas where the yield is very high despite non-palpable nodes.

Superior vena cava syndrome should be mentioned specifically as another indication for mediastinoscopy despite its forbidding clinical picture. Tissue

confirmation before radiotherapy and or chemotherapy is desirable but may not be obtained by standard technics. Cervical nodes may be enlarged due to lymphatic and vascular engorgement but prove to be negative on biopsy. Successful mediastinoscopy in the face of superior vena cava syndrome has been reported by Jepsen (7), Goldberg (11) and Pearson (10) and we have performed it four times without difficulty, obtaining a positive biopsy each time.

Paratracheal cystic lesions appear to be a therapeutic indication for mediastinoscopy. We have successfully extirpated two such cysts, obviating the need for open thoracotomy and two other such cases have been reported (12).

There seem to be no absolute contraindications to mediastinoscopy other than the general condition of the patient.

RESULTS

Fifty mediastinoscopies were performed (Table I).

There were 30 cases of primary lung cancer representing 60% of the total group. Metastatic mediastinal lymph nodes were found in 18 of the 30. Thirteen of the 18 right-sided tumors yielded positive biopsies, while only 1 of the



FIG. 5. Case 4. Squamous cell carcinoma. Small primary tumor right lower lobe. Prominent right hilar and paratracheal adenopathy.

TABLE I
Mediastinoscopy: Summary of Fifty Cases

<i>Diagnosis</i>	<i>No. Cases</i>	<i>Positive Biopsy</i>
Primary lung cancer.....	30	18
Metastatic malignancy.....	3	1
Hodgkin's disease.....	3	2
Sarcoidosis.....	2	2
Tuberculosis.....	2	2
Paratracheal cyst.....	2	2
Malignant thymoma.....	1	1
Reticulum cell sarcoma.....	1	1
Lymphosarcoma.....	1	0
Visceral pleural tumor.....	1	1
Neurofibroma vagus nerve.....	1	0
Giant pulmonary arteries.....	1	0
Undetermined.....	2	0
Total.....	50	30



FIG. 6. Case 5. Adenocarcinoma. Primary peripheral tumor right upper lobe and right paratracheal adenopathy. Resection after preoperative radiation.

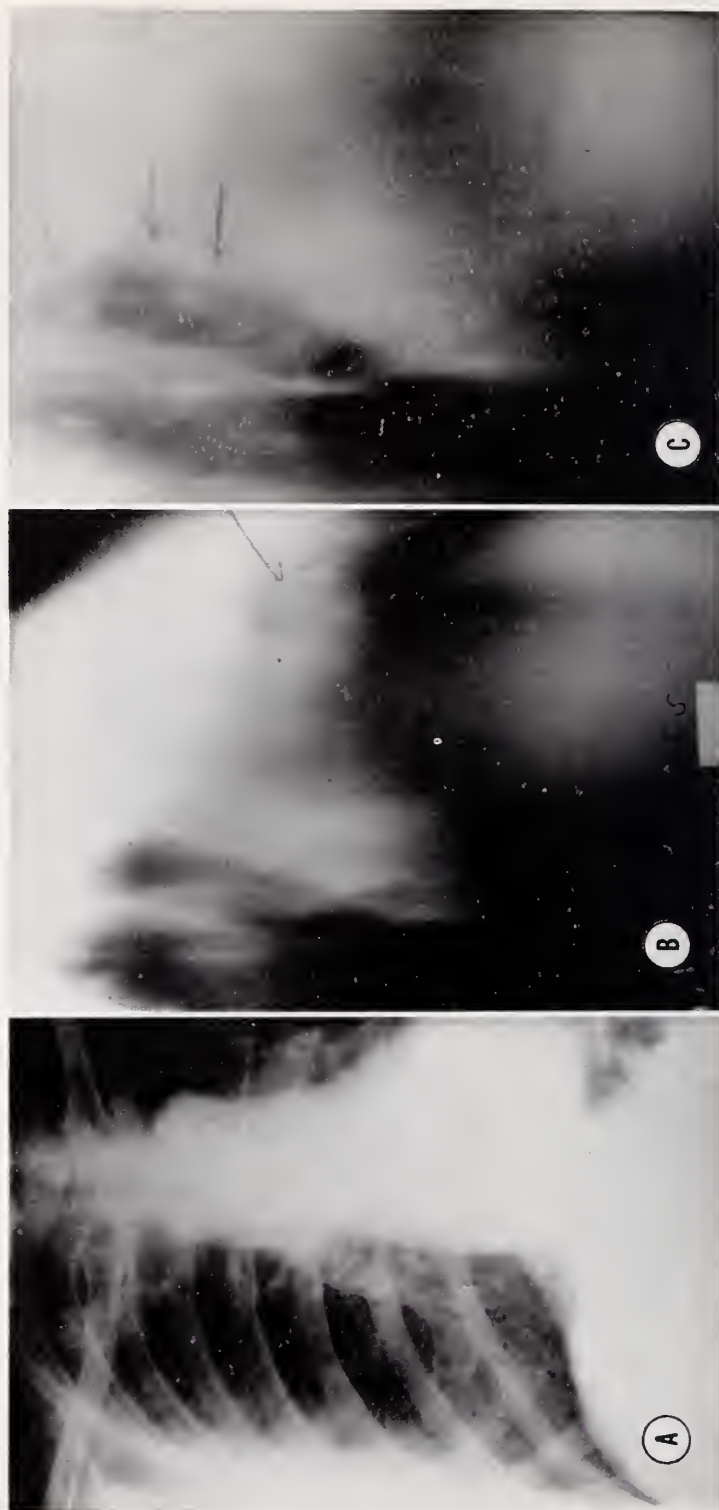


FIG. 7. Case 6. Malignant thymoma. A. Chest x-ray film showing mediastinal enlargement and right parietal pleural scalloping. B. Lateral tomogram showing anterior mediastinal mass. C. Lateral tomogram showing paratracheal nodules. Biopsy from here.

8 left-sided tumors were positive. The site of the primary lesion could not be determined in four cases. Seventeen of the 18 positive biopsies came from the right paratracheal or pretracheal nodes including the single positive obtained in the left-sided growth. The eighteenth biopsy was taken from the subcarinal group of nodes.

Ten patients with negative biopsies underwent thoracotomy. All four right-sided tumors and four out of six left-sided tumors were resectable.

Four patients with primary right upper lobe cancer and positive right paratracheal nodes were subjected to preoperative radiotherapy and then operated.

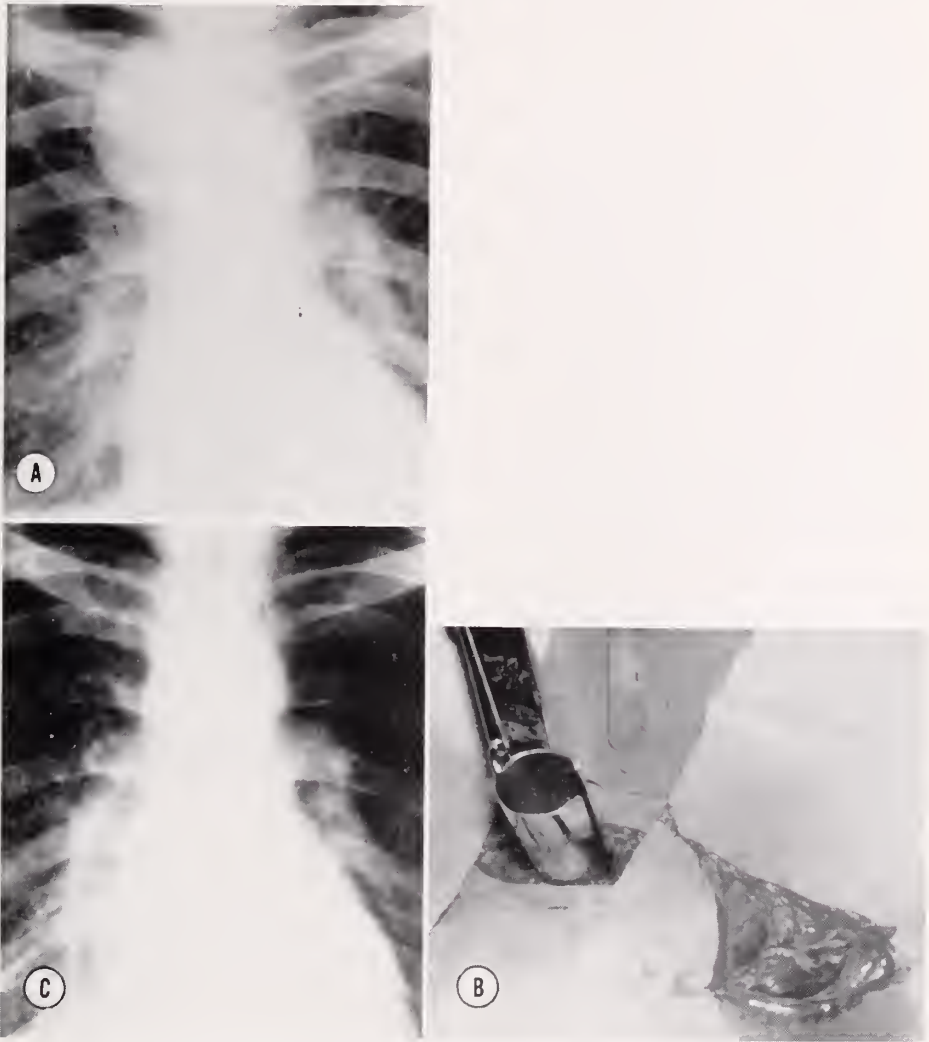


FIG. 8. Case 7. Paratracheal cyst. Resection through mediastinoscope. A. Preoperative chest x-ray film showing right paratracheal mass. B. Mediastinoscopy in progress. Note fluid in syringe aspirated from cyst and the excised specimen (*opened*). C. Postoperative chest x-ray film. Normal.

In three, right upper lobectomy was easily accomplished, the mediastinum yielding negative biopsies at thoracotomy. One of these patients is living and well one year later. The fourth case was technically resectable with a grossly normal mediastinum but lobectomy was abandoned because of the discovery of lymphangitic metastases in the lower lobe.

The lack of positive biopsies from the left paratracheal area in lung cancer appears to be related to the paucity of nodes in this region and to the inability to reach the left para-aortic nodes because of the interposed carotid and subclavian arteries. The neurofibroma of the right vagus nerve was palpable but not biopsied. One of the three patients with Hodgkin's disease had suggestive but inconclusive findings in the specimens, but three months later developed positive cervical nodes. The patient with giant pulmonary arteries was originally thought to have hilar adenopathy. Subsequent cinefluorography showed pulsatile vessels.

Both cases of sarcoidosis had negative Kveim tests, non-palpable cervical nodes but positive mediastinoscopies.

Mediastinoscopy was combined with scalene biopsy seven times, bronchoscopy ten times, thoracotomy three times and bronchoscopy *and* thoracotomy three times, all without complications. A combined unified diagnostic and therapeutic approach is being undertaken with increasing frequency.

The two cases of paratracheal cysts represent therapeutic aspects of mediastinoscopy as both were excised by this method obviating thoracotomy.

Superior vena cava syndrome is not a contraindication to mediastinoscopy. It was safely and successfully performed in four patients; two with Hodgkin's disease and two with carcinoma.

Scars of previous thyroidectomy did not interfere.

A total of 30 definitive positive biopsies were obtained in the 50 cases, 27 of which came from the right paratracheal area.

COMPLICATIONS

Mediastinoscopy is well-tolerated. Patients are ambulatory within twelve hours and may be discharged in two or three days if no further need for hospitalization exists. Skin sutures are removed in three days and radiotherapy may be started promptly. Substernal discomfort, sore throat and stiff neck are common, but transient and mild.

Six complications occurred. There were three cases of right pneumothorax, one of which required a chest tube. One patient bled from a vessel in the skin edge. Tumor implanted in the wound in one case. Chylothorax of 200 cc was encountered at thoracotomy three days after a mediastinoscopy at which considerable dissection was done. The chyle was noted to issue through a pinhole perforation of the mediastinal pleura. It did not reaccumulate after right upper lobectomy.

There were *no* instances of mediastinal hemorrhage, mediastinitis, recurrent nerve paralysis, wound infection or tracheal or esophageal injury.

No deaths occurred.

SUMMARY AND CONCLUSIONS

A discussion of the background, rationale and technique of the Carlens mediastinoscopy has been presented together with a report of fifty cases.

Mediastinoscopy has proved to be a valuable diagnostic and prognostic procedure for certain cases of thoracic disease, particularly lung cancer.

It is a simple, safe procedure, with practically no contraindications and can be performed even in the presence of superior vena cava obstruction.

Two benign paratracheal cysts were removed using this procedure.

Seven cases are summarized to illustrate the value and scope of mediastinoscopy.

Case 1

A 50 year old Negro man was admitted with a three month history of cough, chest pain, dizziness, night sweats, feverishness and weight loss of 2 lbs. Upon physical examination, the only specific finding was bilateral clubbing of fingers and toes. Throughout his hospital stay he was febrile with range of temperature 102 to 104 daily. Chest x-ray film (Fig 2a) initially showed left hilar adenopathy and mediastinal nodal involvement. No parenchymal lesion was seen. He underwent exhaustive diagnostic tests including a left scalene biopsy on September 23, 1965 all of which was unrevealing. Subsequent chest x-ray films in early October (Fig 2b), six weeks after admission, now showed right paratracheal adenopathy as well.

On October 8, 1965 a right scalene biopsy and mediastinoscopy was carried out. The scalene nodes were negative, but the *right* paratracheal node, which was removed intact from the mediastinum, showed metastatic adenocarcinoma (Fig 2c).

Comment. In Case 1 the histological diagnosis of carcinoma was obtained by mediastinoscopy although the findings from bilateral scalene biopsy had been negative. An occult lung cancer is presumed to be the primary tumor.

Case 2

A 72 year old white man had an asymptomatic right paratracheal mediastinal mass for five years, since 1960 (Fig 3a,b). The mass enlarged steadily. No diagnosis had been made in the course of exhaustive examination. No parenchymal lesion was seen.

Mediastinoscopy and bronchoscopy was performed at the same sitting on November 29, 1965. A biopsy of anaplastic carcinoma was obtained from the mediastinum. Bronchoscopy showed only extensive pressure by the mass on the lower trachea.

Comment. Despite the asymptomatic five year period, a positive tissue diagnosis could have been made initially in 1960, had mediastinoscopy been available to us at that time.

Case 3

A 37 year old white man presented with a superior vena cava syndrome due to a huge anterior and middle mediastinal tumor (Fig 4). On September 23, 1966 a left cervical node biopsy was performed. At the time of surgery, there was considerable leakage of chylous fluid from dilated lymphatics, as well as oozing from engorged veins. The cervical node was negative. On September 27, 1966 mediastinoscopy was easily accomplished under general anesthesia. No bleeding or lymphatic leakage was encountered. Biopsy of paratracheal mass revealed Hodgkin's disease.

Comment. This is one of two cases in which mediastinoscopy was carried out in the presence of superior vena cava obstruction. In each of these, no difficulties were encountered.

Case 4

A 60 year old white woman was discovered to have a nodule in the posterior basal segment of the right lower lobe and paratracheal mediastinal adenopathy (Fig 5). She was a heavy smoker but had no pulmonary symptoms due to these lesions. Subtotal thyroidectomy had been performed several years before.

Mediastinoscopy and right scalene biopsy were performed on March 14, 1966 with no difficulties from the previous thyroid surgery. The scalene nodes were negative, but undifferentiated squamous cell carcinoma was found in the mediastinal node.

Comment. In this case scalene node biopsy was negative but mediastinoscopy revealed the histological diagnosis. The previous thyroid surgery caused no technical problems.

Case 5

A 57 year old white woman was referred for mediastinoscopy because of the discovery of a right paratracheal mass (Fig 6). Her previous history included thrombophlebitis, bilateral pulmonary infarction, anticoagulant therapy, and inferior vena cava "clipping." On chest x-ray, a persistent right upper lobe density was present in addition to the transient shadows of the infarcts. Mediastinoscopic biopsy on July 1, 1966 revealed metastatic carcinoma in the right paratracheal nodes. A course of preoperative radiotherapy was administered. On October 3, 1966 a right upper lobectomy was accomplished for a peripheral adenocarcinoma. The right paratracheal glands were now negative. She is well one year later.

Comment. Mediastinoscopy provided tissue diagnosis and a guide to preoperative radiation, leading to definitive treatment in a complicated case. It is believed that the phlebitis and multiple pulmonary emboli were systemic manifestations of the small carcinoma in the right upper lobe.

Case 6

A 63 year old man had a history of vague chest complaints for several months. X-ray films revealed an anterior mediastinal shadow, scalloping of the right parietal pleura and masses around the lower trachea best noted on tomography (Fig 7a,b,c). A clinical diagnosis of thymoma with metastases was made.

On January 3, 1966 right scalene biopsy and mediastinoscopy was performed. The former was negative but the latter revealed metastatic malignant thymoma in the paratracheal area.

Comment. With increased experience, we would have omitted the scalene biopsy. Mediastinoscopy provided a diagnosis that might otherwise have been made by open thoracotomy or anterior mediastinotomy.

Case 7

A 23 year old white man, asymptomatic, had a routine chest x-ray film taken because of the discovery of a positive tuberculin skin test. A right paratracheal mediastinal mass was found (Fig 8a).

Mediastinoscopy performed April 11, 1966 revealed a paratracheal cyst. This was completely removed through the cervical incision (Fig 8b). He made an uneventful recovery (Fig 8c).

Comment. This represents one of two cases in which excision of a paratracheal cystic lesion was accomplished without difficulty by means of mediastinoscopy.

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Postsympathectomy Neuralgia

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The occurrence of intense, aching thigh pain shortly after sympathectomy for occlusive vascular disease is well recognized by all vascular surgeons (1-5). It is said that this pain, which is referred to as postsympathectomy neuralgia, is unrelated to any major neurological manifestations (1, 2). Few, if any, of the patients reported in the literature, however, have had adequate neurological examinations or investigations. The purpose of this communication is to report four patients with this condition who were seen in neurological consultation. Abnormal neurological findings were found in three of these patients. Electromyography, conduction velocity studies and lumbar punctures were performed in two patients.

CASE REPORTS

Case 1: In November 1963 a bypass graft was performed for a completely occluded right femoral artery in this 51 year old white woman. Her symptoms of claudication returned, however, due to closure of the arterial bypass. She was hospitalized again in March 1964. A right lumbar sympathectomy (second, third, and fourth lumbar segments) was performed on March 17, 1964. One week later she noted severe pain at the right buttock, which radiated to the right posterior thigh. This intensified and she was unable to walk.

She was seen by a neurologic consultant on March 30. There was definite paresis of the right quadriceps and right iliopsoas muscles. The right knee jerk could not be elicited and there was hypalgesia on the anterior surface of the right thigh and medial aspects of the right knee and leg. The remainder of the neurological examination was normal.

A lumbar puncture, including manometric study of the spinal canal, gave normal results. Roentgenograms of the lumbar spine were also normal. Her pain was severe enough to require narcotics. Improvement over the next three weeks was sufficient to permit discharge, but some pain persisted. This gradually subsided over the next six weeks. She was re-hospitalized in January 1965 for an unrelated condition. There were no neurologic symptoms and the neurologic examination was normal.

Case 2: A 64 year old white man was hospitalized in March 1965 because of intermittent claudication of the left calf. An angiogram revealed extensive disease involving aorto-iliac and femoral popliteal vessels and a complete occlusion of the superficial femoral artery. A left lumbar sympathectomy (L2, 3, 4) was performed on March 4, 1965. Eleven days later he noted the onset of severe pain at the left buttock which radiated down to the left calf.

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Detailed neurologic examination was performed on March 24, 1965. There were no definite motor or sensory findings, but the left knee jerk was significantly reduced as compared to the other deep tendon reflexes. There was some increased pain on left straight leg raising to about 40°.

The cerebrospinal fluid was normal. An electromyogram revealed normal potentials in the left quadriceps and anterior tibialis and in the abductors of the left thigh. Conduction velocity was normal in the left peroneal nerve.

The patient's pain subsided gradually over the next four weeks, and when readmitted in December 1965, there were no neurologic symptoms or signs.

Case 3: A right femoral-popliteal bypass was performed in this 65 year old white woman. Her symptoms of claudication in the right thigh continued and she was hospitalized at this institution in June 1966. An angiogram showed a complete occlusion of the right femoral artery, and a right lumbar sympathectomy (L2, 3, 4) was performed on June 20, 1966. One week later she noted pain at the right hip which radiated posteriorly to the right thigh and knee and then anteriorly to the ankle.

Neurological consultation on June 29, 1966 failed to find any abnormalities in the reflexes or any positive mechanical signs. There was some paresis of abduction of the right thigh, however. Pin prick appreciation was diminished along the lateral aspect of the right leg. There were no other neurologic abnormalities.

An electromyogram revealed normal potentials in the right anterior tibialis, and conduction velocity was normal in the right peroneal nerve.

She subsequently developed a tender swelling in the right thigh, which was due to an abscess from the previously inserted infected graft. The relationship between the radiating pain and this abscess is uncertain, but the abscess was noted three weeks after discharge, about the time the pain of "neuralgia" was subsiding.

Case 4: A 66 year old man had a ten year history of bilateral claudication. An aortogram revealed occlusions of the left common iliac and right superficial femoral arteries. Bilateral lumbar sympathectomies (L2, 3, 4) were performed on August 25, 1966.

Three days later he noted pain at both mid-posterior thigh regions which radiated laterally down to both ankles. This pain was increased with activity.

The neurological examination was completely normal and there were no mechanical signs. Symptoms gradually subsided over the next five weeks.

DISCUSSION

Postsympathectomy neuralgia has been reported to occur in 2.4% to 67% of patients undergoing sympathectomy (3). The four patients reported here were the only possible cases of the syndrome among 200 patients who underwent sympathectomy performed by one of us. Although neuralgia is reported more frequently with high—as compared to low—lumbar sympathectomy (4), all of our sympathectomies involved the second to fourth lumbar segments.

This pain, which is quite severe, and does not respond to narcotics, local heat, ice, etc., is said to occur suddenly, about one to two weeks postsympathectomy (1, 3), to involve the thigh primarily, and to disappear just as rapidly after a few days to several months (1, 3). The symptoms began suddenly in all four of our patients, from three to eleven days after sympathectomy. The pain radiated to the ankle or calf in three of these patients. All four patients had pain which subsided gradually from four to nine weeks after onset. The mode of disappearance of pain in this report differs somewhat from that previously reported. The spontaneous although gradual cessation of pain is indeed fortunate, since therapy is so ineffective.

Another apparent discrepancy between the patients in this series and those reviewed in the literature is the radiation of pain down to the legs in three patients in this report. The pain previously was said to occur only in the thighs (3) or in a distribution of the first three lumbar dermatomes (1, 4), which would apply to Case 1 only. We do not believe that Cases 2, 3 and 4 had any condition other than postsympathectomy neuralgia to explain the radiation of pain to their legs.

Although previous reviews of the syndrome have emphasized the lack of any major neurological findings on examination, occasional reports of "hyperalgesia" (4), "hyperesthesia" (1) or a resemblance to meralgia paresthetica (3) have appeared. A diminution to absence of the knee jerk, diminished sensation, and weakness of specific muscles were each found in two of our patients. Although femoral nerve involvement was suggested by Case 1, and possibly Case 2, no definite localization was possible in the other patients. The signs in Cases 1, 2 and 3 seemed quite definite, were not related to limitation of motion because of a pain, and their presence does suggest that neurological findings may be not uncommon in patients with postsympathectomy neuralgia.

Unfortunately the investigations of conduction velocity, electromyography and cerebrospinal fluid failed to confirm or explain the neurologic abnormalities. It should be noted that the electromyograms were performed eight days (Case 3) and sixteen days (Case 2) after the onset of neurologic symptoms, thus probably excluding a too early application of this technique.

The etiology of postsympathectomy neuralgia is still unknown. Its occurrence is probably unrelated to operative technique (1). Retraction or other trauma to the genitofemoral (3) or other nerves of the lumbosacral plexus can probably be excluded by the clinical differences, including the time of onset of symptoms, between this syndrome and those which follow pelvic surgery. This syndrome is usually unrelated to activity and therefore not the so called "hip claudication" due to arterial insufficiency of the iliac arteries. Ischemic neuritis, ganglioneuritis from retroperitoneal inflammation, pathologic vasodilatation, neuroma formation, increased sensitivity of somatic nerves and several other mechanisms have been suggested in an attempt to explain postsympathectomy neuralgia (1-5). The absence of fever and other systemic symptoms made infection an unlikely etiologic possibility, although

it cannot be excluded in Case 3. No conclusions can be drawn from the data on our four patients as to possible pathogenesis of the syndrome.

SUMMARY

Four patients with postsympathectomy neuralgia are described. Abnormal neurological findings were present in three. These included diminished to absent knee jerk in two; diminished sensation on the anterior or lateral surfaces of the thigh and medial surfaces of the leg in two; paresis of the abductors of the thigh in one; and paresis of the iliopsoas and quadriceps muscles in one. Electromyography, conduction velocity studies and cerebrospinal fluid tests gave normal results. In three patients the pain radiated from the thigh down to the leg, and all tended to improve slowly. The onset of symptoms occurred from three days to two weeks post-sympathectomy, and lasted from four to nine weeks. The incidence of postsympathectomy neuralgia is about 2%. Perhaps further neurologic study and investigation of this rare syndrome may give some information as to its etiology, which at present is unknown.

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Carcinoma of the Male Breast

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Carcinoma of the male breast is regarded as a relatively rare tumor. In the United States in the year 1964 there were 25,936 deaths recorded in the female population due primarily to breast cancer (1). This is an incidence of 26.6 per 100,000. During the same year, there were 226 deaths in the male population due to primary breast cancer; an incidence of 0.2 per 100,000. Male breast carcinoma has been reported to vary from 0.9% to 2.2% of large breast cancer series (Table I).

This type of malignancy is often thought of as a disease of older men (2). Nathanson and Welch (3) reported the mean age to be 64 years. However, Treves and Holleb (4), in reporting on 146 cases, the largest series of such tumors to date, note an average age of 52 years with patients ranging from 24 to 85. Ten of their patients were 40 years old or younger; two were in their late 20's. The youngest patient reported is a 12 year old boy (5) while the oldest patient noted in the literature is a 93 year old man (6).

STUDY

In the past 13 years at The Mount Sinai Hospital there were 21 cases of primary breast carcinoma observed in white males. They ranged in age from 39 to 75 years. Various types of occupations were noted but there did not appear to be any correlation between occupation and the development of breast cancer.

The most common single sign noted by the patient was a painless lump in the breast. Table II reveals that this occurred in 12 of the 21 patients; an incidence of 57%. The next most common sign was nipple retraction associated with the breast mass. This was present in six cases (28%). There was one case in which pain was noted in conjunction with a mass and nipple retraction; one case of mass plus nipple retraction and discharge; and one case of mass plus nipple discharge. Nipple retraction was, therefore, present in eight cases while nipple discharge was noted in two cases.

Three cases had a prior history of having a malignancy. One had primary carcinoma of the prostate, one had primary carcinoma of the colon and one had carcinoma of the breast. None of the patients offered any history of trauma to the breast as a possible etiological cause. There was no case of preceding gynecomastia. One patient had received prior hormonal treatment.

Table III illustrates that 13 of the cases were categorized as clinical Stage I tumors prior to surgery. Three of the 13 cases were revealed to be pathological Stage II tumors on the basis of positive axillary lymph nodes. There were four patients classified as Stage II on clinical examination because of the sus-

From The Breast Clinic, Department of Surgery, The Mount Sinai Hospital, New York, N. Y.

TABLE I
Male Breast Cancer Statistics (From Lewison¹¹)

Report	Total Breast Cancer	Male Breast Cancer	Per Cent
Williams.	1,879	16	0.9
Finsterer	692	11	1.6
Geschickter	2,554	30	1.2
Lewis and Rienhoff	950	9	0.9
Jaaskelainen . . .	1,190	13	1.1
Payson and Rosh	1,141	25	2.2

TABLE II
Cancer: Signs and Symptoms of Male Breast Cancer

Presenting Signs and Symptoms	Cases
Mass alone	12
Mass plus nipple retraction	6
Mass, nipple retraction and pain	1
Mass, nipple retraction and nipple discharge	1
Mass plus nipple discharge	1

TABLE III

	Clinical Stage	*Pathological Stage
Stage I	13	10
Stage II	4	5
Stage III	0	0
Stage IV*	2	0

* 2 patients received no surgical treatment; 1 patient had bilateral orchiectomy, 1 patient had simple mastectomy without axillary dissection.

picion of having positive homolateral axillary lymph nodes. Two of these cases were proven to be pathological Stage II carcinomas; one case was a Stage I due to negative axillary nodes and one case signed out of the hospital prior to definitive treatment. There were no cases which were clinically classified as Stage III. However, there were two cases of clinical Stage IV carcinoma noted. One underwent a bilateral orchiectomy but died within one year. The other patient died in the hospital prior to treatment.

The pathology of the male breast tumors was similar to that of the female breast tumors as seen at The Mount Sinai Hospital; Table IV shows that 13 patients had scirrhous carcinoma, 3 medullary carcinoma and 3 duct cell carcinoma. One of the patients designated as having duct cell carcinoma was reviewed and later reclassified as "adenomatous hyperplasia with malignant potential."

The primary treatment afforded these patients was radical mastectomy,

TABLE IV
Histological Diagnosis

Histological Diagnosis	Cases
Scirrhou carcinoma	13
Medullary carcinoma	3
Duct cell carcinoma	3*

* 1 case reclassified as "adenomatous hyperplasia potentially malignant."

TABLE V
Treatment

Primary Treatment	Cases
Radical mastectomy	11
Radical mastectomy with skin graft	3
Simple mastectomy	3
Simple mastectomy with skin graft	1
Bilateral orchiectomy	1
No surgical treatment	2*

* 1 case left hospital against advice, 1 case died in hospital prior to treatment.

as noted in Table V. Fourteen of the 21 patients underwent such a procedure: 3 of these 14 patients had a radical mastectomy with an autogenous split-thickness skin graft. Four patients had a simple mastectomy; one had a concomitant skin graft. One patient with a Stage IV tumor had a bilateral orchiectomy while two patients did not receive operative treatment.

Of the 14 patients who underwent primary treatment of radical mastectomy, 8 (57%) were Stage I on pathological study, while 6 (43%) were noted to be Stage II on the basis of involved axillary lymph nodes. Seven of the eight Stage I patients had a pathological diagnosis of scirrhou carcinoma; one was duct cell carcinoma. Four of the patients with Stage I scirrhou carcinoma are well with no evidence of recurrent disease; one patient shows evidence of axillary and skin recurrence; two patients died, one four years after surgery, the other three years after treatment. The patient with duct cell carcinoma is well 12½ years after radical mastectomy.

Six patients with a pathological Stage II tumor had radical mastectomy as primary treatment. There were four cases of scirrhou carcinoma and two cases of medullary carcinoma. One patient with scirrhou carcinoma is well with no signs of recurrence, while the other three cases show clinical evidence of metastases. Both patients with medullary carcinoma have died, one 6 years and eight months after surgery, the other patient 11 years and two months following surgery.

Four patients had simple mastectomy as primary treatment for breast cancer. There was one case of scirrhou carcinoma, one medullary carcinoma, one duct cell carcinoma and one duct cell carcinoma later classified as adenoma-

tous hyperplasia. None of these patients had complete axillary dissection. No case was noted to have axillary lymph nodes involved. The patient with scirrhous carcinoma is well without signs of recurrence four and one-half years following surgery. The patient with medullary carcinoma is alive and well five years and three months after surgery. The patient with duct cell cancer died from severe cardiac disease within two months after surgery. The patient with adenomatous hyperplasia is alive and well.

Data of 19 of the 21 cases was available for follow-up analysis. At present nine of these patients are well with no evidence of recurrence; three are alive with clinical evidence of recurrent disease and seven have died of their disease. One patient signed out of the hospital after refusing treatment and one patient has been lost to observation.

Of the 13 cases with scirrhous carcinoma as the primary breast pathology, 6 are alive and well. Five of the six cases were pathological Stage I tumors while one had positive axillary lymph nodes. The average survival time to date of these six cases is 47 months. The Stage II patient has lived 45 months to date without recurrence.

Three patients are alive with clinical evidence of recurrence; two of the three cases had homolateral axillary lymph nodes involved at the time of their primary surgery. One patient had a clinical and pathological Stage I tumor. This was a 69 year old white man with a two week history of noting a hard, stony 3 by 5 cm mass over the right breast. He underwent a right radical mastectomy with a split-thickness skin graft in October 1963. He was well until November 1965 at which time a recurrence was noted in the homolateral axilla. Metastases were confirmed by biopsy and the patient received radiotherapy. In January 1966 skin recurrence was noted just above the skin graft site. He is at present under hormonal therapy and doing well.

The other two cases, aged 52 and 57 years, were operated upon April 1961 and February 1962 respectively. These patients had radical mastectomies as primary treatment and received postoperative radiotherapy. Presently both are receiving maintenance cancer chemotherapy and hormonal treatment. The average follow-up for these last two cases is 48 months.

One patient operated upon in August 1960 has been lost to follow-up examination. He had a left radical mastectomy with positive axillary lymph nodes upon examination and had received postoperative radiotherapy.

Three patients with scirrhous carcinoma died. One of these patients had a carcinoma of the prostate gland. He underwent radical mastectomy August 29, 1962 and a transurethral resection of the prostate September 10, 1962. Findings were interpreted as primary carcinoma in both sites. The axillary lymph nodes were free of metastases at the time of the radical mastectomy. He developed metastases to the bones and lung within two years and died in the summer of 1965, three years after surgery.

The second case was a 61 year old man who underwent right radical mastectomy in July 1956. He had a six week history of a mass in the right breast associated with nipple retraction. The axillary lymph nodes were not involved.

In March 1959 he was readmitted with metastases to the lung, pelvis and spine. He received radiotherapy and steroid treatment but died in the summer of 1960, four years following surgery.

The third case was a 67 year old man with a history of a left breast mass for 2 years prior to hospital admission. Biopsy performed on admission in July 1963 revealed scirrhous carcinoma. He had a 3 cm hard mass adherent to the left areola with nipple retraction and fixed to the underlying pectoralis major fascia. The left axillary nodes were described as palpable, matted and fixed. He had metastases to the lungs and bones. Treatment consisted of a bilateral orchiectomy plus cancer chemotherapy, steroids and radiotherapy. He died in March 1964, eight months after primary therapy was started.

Three patients had medullary carcinoma of the breast; two have died, one is alive and well without any evidence of disease. The latter is a 74 year old man who had a mass in his right breast for approximately 1 year prior to admission. He was classified as clinical Stage I breast cancer. He had a simple right mastectomy with a low axillary dissection in January 1961. Pathological diagnosis was medullary carcinoma with negative axillary lymph nodes. He has been well in the interim with no evidence of recurrence to date, 5½ years after surgery.

Of the two patients who have died, one was a 60 year old man with a three week history of a nodule in the right areola. Clinically, he presented as a Stage I carcinoma and he had a right radical mastectomy in March 1954. Operation revealed a medullary cancer with involved lymph nodes. He was relatively well for three years and then developed abnormal neurological signs and was thought to have cerebral metastases. He died in November 1960, 6½ years after surgery. Post-mortem examination revealed the neoplasm in the right side of the brain to be a benign meningioma. There were no signs of metastases from the primary breast cancer.

The other case concerned a 39 year old schoolteacher with a four week history of mass in the left nipple associated with nipple retraction and localized pain. He had a left radical mastectomy in October 1954 at which time the axillary lymph nodes were involved with metastases. He remained in good health until December 1963 at which time metastases were noted to the ribs and lung. He received treatment with radiotherapy and steroids. In September 1964 he had destructive lesions in the spine, hip and thigh, and again received radiotherapy. He expired in December 1965, 11 years after surgery.

Three patients in this series had duct cell carcinoma of the breast; one is alive and well; one died during hospitalization from severe cardiac disease after a simple mastectomy; one, whose pathological findings were reclassified as "adenomatous hyperplasia with malignant potential," is alive and well.

The first patient is a 44 year old clerk with a two month history of mass in the left breast associated with nipple discharge and retraction. He had a left radical mastectomy in October 1953 with a concomitant autogenous split

thickness skin graft. Axillary lymph nodes were free of disease. He is at present without evidence of recurrence, 12½ years following surgery.

The second patient was a 52 year old executive with a three month history of a 1.5 cm cystic mass in the right breast. He had severe cardiac disease and was under anticoagulation treatment. A needle aspiration biopsy confirmed the diagnosis of duct cell carcinoma. A right simple mastectomy was performed in October 1958 without axillary dissection. The patient died within one month of cardiac disease.

The third patient is a 60 year old broker with a past history of treatment in 1957 with an unknown type of hormone for fatigue. In 1958 he noted a mass in the right breast and a right simple mastectomy was performed at another hospital. The diagnosis was noninfiltrating duct cell carcinoma. At that time the left breast was noted to be swollen but no biopsy was performed. It was also noted that he had hepatitis in 1949. In December 1962 he noted nodules under the left areola. A left simple mastectomy was done for what was called a duct cell carcinoma. On review of the pathology slides from 1958 and 1962 the diagnosis was reclassified as "adenomatous hyperplasia with malignant potential." This patient has been well with no evidence of recurrence to date.

DISCUSSION

The largest series of male breast cancer recorded in the literature to date is that of Treves and Holleb (4). They reviewed 146 cases treated in the Memorial Hospital in New York City from 1924 to 1954; a 30 year period with an average of 5 male breast cancer cases per year. Their patients ranged in age from 24 to 85 years. Ten of the men were 40 years old or younger with 2 of them in their 20's. The average age of their patient was 52 years.

Nathanson and Welch (3) regard male breast cancer as a disease of older men and report an average age of 64 years. The youngest patient recorded is the case of a 12 year old boy (5) while the oldest case is that of a 93 year old man (6).

The series of male breast cancers in The Mount Sinai Hospital ranged in age from 39 to 75 years of age with the average age 58. The left breast was more frequently involved than the right breast, as is the case in the female. Treves (4) reported 82 left sided breast cancers and 63 on the right side, with 2 cases of bilaterality. The Mount Sinai Hospital series had 11 left side, 9 right side and 1 bilateral case.

Three patients in this series (14%) had a history of preceding malignancy. One had prostatic carcinoma, one had carcinoma of the colon and one had duct cell carcinoma of the breast. Treves and Holleb (4) recorded 10 patients with related malignancies; 3 prior to development of breast cancer (1 colon, 2 lymphosarcomas); 2 cases with simultaneous cancers (1 prostate, 1 buccal mucosa); and 5 subsequent to development of breast cancer (1 rectal,

1 lingual, 1 lymphatic leukemia, 2 basal cell carcinoma of face). This represented a 14.6% relationship of malignancies associated with primary male breast cancer.

There was no apparent relationship of occupation to the development of male breast carcinoma. Due to the susceptibility of the male breast to trauma one might make a case for an etiological factor. This is not borne out in a review of the literature. Most investigators feel that the trauma only serves to bring a preexisting breast mass to the attention of the patient (7). However, Gilbert (8) has noted a 29% incidence of previous injury in his male breast cancer patients. Wainwright (9) relates a case of breast cancer resulting from a sword thrust in the chest. Peck (10) reported a case of breast cancer related to an automobile injury in which fractured ribs occurred beneath the subsequently involved breast. Lewison (11) reports on a case of a 12 year old boy who developed breast carcinoma following a golf ball injury to his breast. None of the patients in the Mount Sinai Hospital series offered a history of preceding trauma to the chest wall as a possible cause of the breast mass.

Mammary carcinoma in male mice has been induced by the administration of estrogenic substances (12). Many papers have attempted to relate the administration of estrogenic hormones to the development of male breast cancer. Gilbert (8) collected 11 cases of male breast cancer occurring during estrogenic treatment for prostatic carcinoma. Some investigators have reported on bilateral breast cancer occurring during stilbestrol therapy (13-16). However, Campbell (17) in reviewing this subject feels that the breast cancer in this type of patient is in reality metastatic prostatic cancer, a view strongly supported by Haagensohn (18). Nevertheless, it has been recorded that carcinoma of the male breast in man with the Klinefelter's Syndrome is similar to that in women and is 66.5 times higher than in the general male population (19).

It appears that men with breast cancer delay longer than women with similar disease (18). The average duration of the male breast tumors in Wainwright's series was 2.4 years (9). In Treves series, 13% of the patients had their tumor for at least 4 years prior to seeking treatment. In Haagensohn's series of 16 incidences of male breast carcinoma reported from the Presbyterian Hospital in New York, two patients had preceding documented histories of seven and eight years respectively of noting a breast mass. The delay in seeking medical attention in the Mount Sinai Hospital series ranged from 10 days to over four years. The average delay was seven months; two of the patients noted a breast mass for an indeterminate number of years. Treves recorded an average delay of nine months in his patients.

As is seen in Table V primary treatment included radical mastectomy, simple mastectomy, and bilateral orchiectomy. None of the patients were primarily treated with radiotherapy, cancer chemotherapy or adrenalectomy. There has been marked clinical improvement in metastatic breast cases in the male treated by bilateral orchiectomy following the initial report by

Farrow and Adair (20). In the past decade, bilateral adrenalectomy has also been followed by marked clinical remissions in selected cases (21-23).

The five year overall survival rate of the Mount Sinai Hospital series reveals 12 of 19 cases followed to be alive at present. Of these 12 cases, 3 have clinical evidence of recurrence, while the other 9 patients are alive and well without sign of recurrence. The five-year survival rate was 63% while the absolute five-year survival rate was 43%. Treves reported 29% absolute five-year survival rate and 44% overall five-year survival rate. Huggins had a five-year survival rate of 20% absolute.

In the Mount Sinai Hospital series, 6 of the 21 cases had palpable axillary nodes prior to surgery, a 29% incidence. Palpable axillary lymph nodes were present in over 72% of Huggins series and in 60% of Treves patients. The delay in seeking medical attention plus the high incidence of palpable and often involved axillary lymph nodes is probably a factor in explaining the relatively poor prognosis for men with primary breast cancer.

SUMMARY

1. Breast cancer is a rare malignancy in the male. Male breast cancer accounted for 226 deaths in the male population of the United States in 1964; an incidence of 0.2 per 100,000. During the same year 25,936 women died from breast cancer; an incidence of 26.6 per 100,000.

2. A 13-year experience with carcinoma of the male breast is presented from The Mount Sinai Hospital. Twenty-one cases were observed during this period. Patients ranged in age from 39 to 72 years. All were white. The average age was 58 years. The left breast was the site of cancer more often than the right breast.

3. A painless mass in the breast was the most common clinical sign. This was present alone or in combination with nipple retraction, nipple discharge. The average delay in seeking medical attention was seven months, with a range of ten days to over four years.

4. Scirrhus carcinoma was the most common histological finding. There were 13 such cases as well as 3 cases of medullary carcinoma and 3 cases of duct cell carcinoma.

5. Primary treatment offered was radical mastectomy in 14 cases, simple mastectomy in 4 cases and 1 case of bilateral orchiectomy: 2 cases were not treated surgically.

6. The 5-year survival rate of The Mount Sinai Hospital series was 63%; the absolute rate was 43%.

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The Porphyrrias. A Clinical Review

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The porphyrias are inherited and acquired diseases characterized by overproduction of porphyrins and their precursors, and the variable occurrence of typical cutaneous lesions and acute attacks. Ignorance of the actual biochemical lesions and inconstant nomenclature have given rise to numerous classifications. It is the purpose of this paper to summarize the porphyrias, emphasizing clinical features and grouping them as simply as possible with regard to present knowledge, and to list some simple qualitative tests with their indications and limitations.

For subsequent reference, the biosynthesis of heme is diagrammed in Figure 1. The following reactions are particularly noteworthy: (1) The formation of δ -aminolevulinic acid (ALA) is catalyzed by the enzyme ALA synthetase. This is the rate limiting step of the entire sequence of reactions. (2) In the absence of isomerase, the monopyrrole porphobilinogen (PBG) polymerizes to uroporphyrinogen I which cannot be utilized for heme synthesis. (3) With the exception of protoporphyrin IX, all the porphyrins are useless by-products of heme synthesis. The porphyrinogens (reduced porphyrins) are the actual intermediates. See Schmid (1) for a comprehensive discussion of porphyrin metabolism.

ERYTHROPOIETIC PORPHYRIAS

The major subdivision of the porphyrias is based on studies (2) showing that the source of excess porphyrins in Congenital erythropoietic porphyria is the developing erythrocyte, while in other forms of the disease the liver is the primary source. Erythropoietic protoporphyria, described after Schmid, Schwartz and Watson's paper appeared, has been shown to belong in the former category.

Congenital Erythropoietic Porphyria (1)

This rare disease is inherited as an autosomal recessive. Only 60 cases had been reported in the world literature through 1963 (1). A relative deficiency of PBG isomerase in the bone marrow leads to overproduction of biologically useless uroporphyrin I and coproporphyrin I. These compounds impart a pink color (and cause intense red fluorescence under ultraviolet light) to the urine, teeth and bones which is detectable at birth. In conjunction with prolonged solar exposure they cause skin lesions which are most severe in summer and fall. Bullae develop on the exposed parts of the skin and slowly heal to form depigmented scars. Secondary infection leads to contractures and mutilating, atrophic scarring with resorption of distal nose, ears and digits. The epidermis is readily separated from the subcutaneous tissue (Nikolsky sign). Hyper-

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TABLE I
Classification of the Porphyrias

- I. Erythropoietic porphyrias
 - A. Congenital erythropoietic porphyria
 - B. Erythropoietic protoporphyria
- II. Hepatic porphyrias
 - A. Cutaneous porphyrias (Symptomatic porphyria, Porphyria cutanea tarda)
 - B. Acute porphyrias
 - 1. Swedish genetic porphyria (Acute intermittent porphyria, Pyrroloporphyria)
 - 2. South African genetic porphyria (Variegate porphyria, Protocoprotoporphyria)

pigmentation and a lanugo-like hypertrichosis often occur. Splenomegaly and a hemolytic anemia which is generally mild and sometimes intermittent are present in most cases. Because the excess porphyrin production is a function of the rate of erythropoiesis, splenectomy may improve both the anemia and the skin lesions.

Erythropoietic Protoporphyria (3)

Although erythropoietic protoporphyria has been recognized only in the last decade, it is probably one of the more common porphyrias. It is inherited as an autosomal dominant and is characterized by elevated erythrocyte protoporphyrin without anemia. Plasma and fecal protoporphyrin are sometimes elevated; the urine porphyrins and precursors are always normal. Following solar exposure as brief as several minutes, afflicted patients develop intense pruritis and burning of the exposed skin which may be followed by erythema, edema, wheal formation and eczematization. Unlike the other porphyrias, vesicle formation rarely occurs. While many patients first manifest the disease in childhood, others (with unequivocal biochemical evidence of disease) are asymptomatic throughout life. The level of plasma protoporphyrin may determine the severity of the disease in a given patient. Avoidance of sunlight is the only treatment.

HEPATIC PORPHYRIAS

Cutaneous Porphyrias (Symptomatic Porphyria, Porphyria Cutanea Tarda)

The cutaneous hepatic porphyrias are characterized by absence of demonstrable heredity, overproduction of porphyrins (mainly uroporphyrin) by a diseased liver and skin lesions identical to those of Congenital erythropoietic porphyria. Like the latter disease, porphyrin excess may color the urine red, pink or brown. Because these diseases begin in later life, the teeth are not involved. This clinical syndrome has occurred in four different contexts.

1. Chronic liver disease, usually alcoholic. A few drinks will cause increased urinary coproporphyrin in persons with a normal liver, and corprotoporphyrinuria is often demonstrable in patients with chronic liver disease. Because

HEME SYNTHESIS

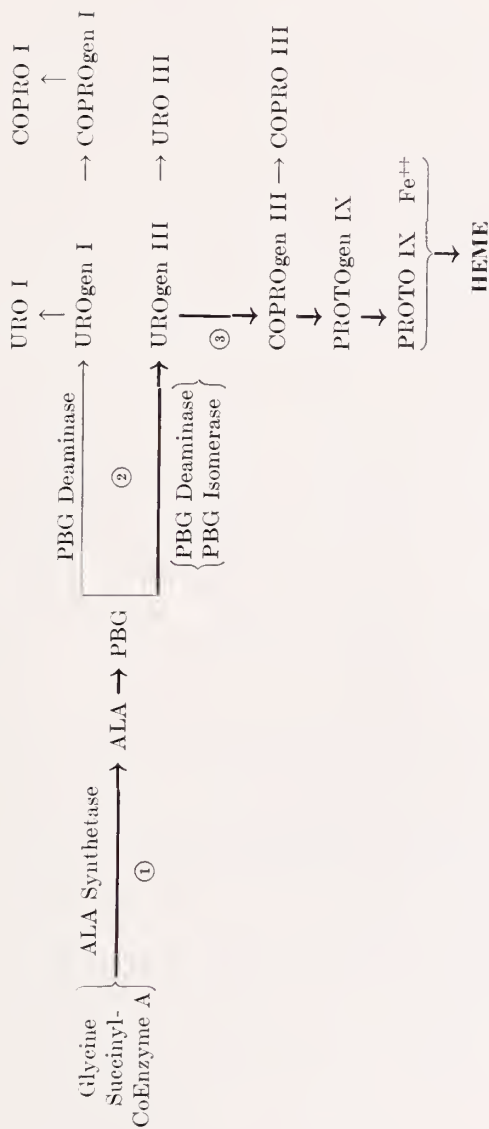


Fig. 1. Heme synthesis. ALA: δ -aminolevulinic acid; PBG: Porphobilinogen; UROgen, COPROgen, etc.: Uroporphyrinogen, etc.; URO, COPRO, etc.: Uroporphyrin, etc.

most cirrhotics do not develop cutaneous porphyria, an underlying genetic defect has been postulated but to date has not been demonstrated.

2. Bantus (4). Cutaneous porphyria is common among the Bantus and the Coloured of South Africa. Its prevalence is greatest among the semicivilized Bantus who live in urban areas and consume large quantities of potent, illegal, homemade liquors ("shimiyane" and "gaveen"). While the disease is clinically indistinguishable from that occurring in white alcoholics, its greater incidence (1% of Bantu outpatients seen at Baragwanath Hospital, Johannesburg (5)) may reflect the ingestion of more potent hepatotoxins, at least with respect to the induction of ALA synthetase (see below). Characteristically, both White and Bantu alcoholics with cutaneous porphyria show clinical improvement and a decline in porphyrin excretion while hospitalized. In the occasional patient who stops drinking, the disease may disappear altogether.

3. Turkish Epidemic (6). During the period 1955-59 an estimated 3000 to 5000 people in southeastern Turkey developed cutaneous porphyria from the ingestion of seed wheat containing the fungicide hexachlorobenzene. (This compound is now used to produce experimental porphyria. Like all other porphyrinogenic drugs, it produces a marked increase in hepatic production of ALA synthetase with consequent overproduction of porphyrins and precursors within hours after its administration to laboratory animals. (7)) Following recognition of the etiologic role of hexachlorobenzene, the Turkish government discontinued its use and the disease gradually disappeared.

4. Hepatoma (8). There is one recorded, well documented case of cutaneous porphyria due to a hepatoma which manufactured large quantities of porphyrins. After the tumor was excised the patient's porphyrin excretion fell and skin lesions disappeared.

Acute Porphyrrias

The classic tetrad of abdominal pain, neuropathy, psychosis and port wine colored urine often fails to develop in an attack of acute porphyria until after the patient has been misdiagnosed and inappropriately, perhaps harmfully, treated. Alertness to the possibility of this condition is the prerequisite for early diagnosis.

Table II summarizes the clinical features of 432 acute attacks from four published series. Attacks rarely occur before puberty and are most frequent in the 20 to 40 age span. There is a tendency to outgrow the disease thereafter so that attacks are very uncommon past age 60, and the disease is sometimes undetectable by biochemical means in aged patients. The mortality of hospitalized patients with acute attacks is around 25%, but many with mild attacks are not hospitalized once the diagnosis has been established. The following have been implicated as precipitating agents: drugs (barbiturates, sulfonamides, griseofulvin, estrogens, Sedormid and other discontinued sedatives), infection, alcohol, mental stress, menses, ovulation and pregnancy. There is an enormous range of individual susceptibility to these factors, but it is safest to proscribe alcohol and all the medications listed.

TABLE II

Clinical Feature of Acute Attacks. Comparison of Four Series(Adapted from Eales et al⁹)

	Author			
	Waldenström	Goldberg	Markovitz	Eales and Linder
Total No. Cases	233	50	69	80
<i>Finding</i>	%	%	%	%
Males	40	38	39	30
Females	60	62	61	70
Abdominal pain	85	94	95	90
Vomiting	59	78	52	80
Mental changes	55	56	80*	55
Constipation	48	74	46	80
Paralysis	42	68	72	53
Hypertension	40	56	49	55
Fever	37	14	36	38
Tachycardia	28	64	51	83
Seizures	10	18	—	12
Sensory loss	9	38	24	15
Diarrhea	9	12	11	8
Azotemia	9	?	67	69
Proteinuria	9	14	—	8
Leukocytosis	7	24	48	20
Amaurosis	4	3	—	3
Cranial nerves	?	29	51	9
ECG abnormalities	?	44	47	23

* Includes epileptiform seizures.

Table II is reproduced with permission from *South African Medical Journal* (36:289, 1962).

Any form of abdominal pain can occur during an attack, but the physical findings rarely conform to the severity of the pain and the WBC count is usually normal (Table II). Pain in the extremities often heralds frank neurologic involvement. Typically, this is a rapidly developing motor neuropathy resembling the Guillain-Barré syndrome. Like the latter disease, acute porphyria can cause bulbar palsy with respiratory paralysis (the most common cause of death in acute attacks) and complete recovery is the rule if the patient survives. Unlike the Guillain-Barré syndrome, the spinal fluid protein is usually normal in acute porphyria.

Electrolyte disturbances occur in about 50% of acute attacks. Among the causes are protracted vomiting, excessive sweating and what appears to be inappropriate secretion of ADH. (Inappropriate fluid administration in the last instance resulted in fatal water intoxication of several patients.) Azotemia can result from muscle wasting, oligemia secondary to vomiting or diarrhea,

obstructive uropathy (atonic bladder) and diminished glomerular filtration rate.

Diagnosis of an acute attack depends on the demonstration of elevated urinary PBG, either by quantitative analysis or by the Watson-Schwartz test (see below). For practical purposes, the diagnosis of acute porphyria in relapse can be excluded if the Watson-Schwartz test, performed on a *fresh* urine specimen, is negative. Fresh urine is often normal in color but darkens on standing as PBG is converted to porphyrins and porphobilin (a brown pigment).

Treatment of an acute attack is essentially symptomatic. Phenothiazines, particularly chlorpromazine, are very helpful in controlling vomiting, agitation and pain. Narcotics and antibiotics can be used if clinically indicated. Tracheostomy and assisted respiration are often required during bulbar involvement. Inappropriate ADH secretion is best treated by fluid restriction. Evidence purporting to show the therapeutic value of vitamins, high carbohydrate intake, purines (inosine and adenosine monophosphate), ACTH and corticosteroids, and chelating agents is unconvincing.

Types of Acute Porphyria

Acute attacks occur in two types of porphyria, both inherited as autosomal dominants and usually undetectable before puberty. In the Swedish variety (Acute intermittent porphyria, Pyrroloporphyria) the urine contains excessive ALA and PBG regardless of whether the patient is symptomatic, the fecal porphyrins are normal or minimally increased and skin lesions do not occur. In the South African variety (Variegate porphyria, Protocopro-porphyria) excess porphyrins are found in the stool at all times. Marked elevation of urinary ALA and PBG occurs only during acute attacks. Patients with Variegate porphyria can be completely asymptomatic ("latent") or have typical porphyric skin lesions (albeit generally milder than in Congenital erythropoietic porphyria) and/or acute attacks. It is likely that occasional reports of families with "Hereditary cutaneous porphyria" are really Variegate porphyria in families where acute attacks had not yet occurred.

The Cause of Symptoms in Porphyria

While porphyric skin lesions are due to the porphyrins' powerful photosensitizing properties, the cause of acute attacks remains unknown. All the findings can be explained on the basis of injury to the somatic and autonomic nervous systems, but thus far none of the compounds present in excess (ALA, PBG or any porphyrin) has been shown to be neurotoxic. In fact, considerable evidence indicates that they are not (1). Alternatively, the massive wastage of ALA and PBG may lead to an acute deficiency of a compound essential to normal neurone function, i.e., a heme containing enzyme. If the nervous system dysfunction is due to lack of such an enzyme, then the biochemical defect must exist in nerve cells as well as hepatocytes. To evaluate this hy-

pothesis, one would have to determine central nervous system ALA synthetase in acute porphyria, something which has not yet been done. (This hypothesis is as unsubstantiated as many of the others currently suggested, such as (A) chronic hyper-ALA-emia is neurotoxic, (B) there is an acute deficiency of acetylcholine, (C) there is an acute deficiency of ATP.)

QUALITATIVE TESTS IN DIAGNOSIS OF THE PORPHYRIAS

Porphobilinogen (simplified Watson-Schwartz test)

To 3 ml of fresh urine add 3 ml of Ehrlich's aldehyde reagent. If a pink or red color appears, shake vigorously with 6 ml of chloroform. The test is positive if the color is not extracted by the chloroform.

The Watson-Schwartz test should be employed whenever acute porphyria is suspected. Positive tests will be found in virtually all symptomatic patients. It is not sufficiently sensitive to exclude latent disease, and therefore is not adequate for family screening. The most common error in performance of this test is failure to extract repeatedly with chloroform when large amounts of urobilinogen are present. (Modifications of this procedure are discussed by Watson et al (10), who call attention to rare false positive reactions not due to urobilinogen. These false reactors can be distinguished from PBG if the aqueous phase is also extracted with n-butanol, for only PBG aldehyde is insoluble in butanol.)

Urine Fluorescence

Pink or red fluorescence of urine under ultraviolet light indicates grossly excessive porphyrins and is highly suggestive of porphyria. Consistently positive tests occur in the cutaneous (symptomatic) porphyrias and Congenital erythropoietic porphyria. Unpredictable results occur in the acute porphyrias. Refinements of this procedure are discussed by Goodman and Lyon (11).

Fecal Porphyrins

Stir a pea size stool sample in 3 ml of a 5:1 mixture of ethyl ether and glacial acetic acid until the solution is light brown. Examine under ultraviolet light. If fluorescence is gray green or yellow, the test is negative. If pink or red fluorescence is seen, decant the solution into a clean test tube and shake for 15 seconds with 1.5 ml of 1.5 N (5%) HCl. Persistent fluorescence in the upper (ether) phase is due to chlorophyll and is not clinically significant; pink or red fluorescence in the lower phase indicates increased coproporphyrin and/or protoporphyrin.

This test (modified from Dean (12)) is positive in latent as well as symptomatic cases of Variegate porphyria, and is therefore excellent for family screening. It is usually negative in Swedish acute porphyria. Because other conditions may cause slightly elevated fecal porphyrins, a positive test should be confirmed by quantitative fecal porphyrin analysis.

Erythrocyte Porphyrins (12)

Add 0.1 ml (2 drops) of blood to 2.5 ml of a 5:1 mixture of ethyl ether and glacial acetic acid. Stir to mix thoroughly then decant into a second tube. Add 0.5 ml of 3 N (10%) HCl and shake vigorously. Definite red or pink fluorescence of the acid phase under a Wood's light indicates excess erythrocyte protoporphyrin and/or coproporphyrin. In a patient with a photosensitive dermatitis it is diagnostic of Erythropoietic protoporphyria. Positive tests in patients without skin lesions may indicate latent Erythropoietic protoporphyria, but also occur in some anemias and lead poisoning.

SUMMARY

The porphyrias are subdivided into erythropoietic and hepatic porphyrias according to the site of excess porphyrin production. The latter group includes the cutaneous (symptomatic) and the acute porphyrias. The hypothesis is proposed that the biochemical defect of the acute porphyrias resides in neurones as well as hepatocytes.

Typical porphyric skin lesions may appear in all the porphyrias except Erythropoietic protoporphyria, where there is a distinct cutaneous syndrome, and Swedish acute porphyria, in which skin lesions do not occur. Skin lesions are associated with and caused by increased levels of porphyrins, while acute attacks are associated with but not caused by increased ALA and PBG.

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Computerization of Serial Records in the Medical School Library

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My purpose is to build upon the foundation of the work which has been done in the area of computerized serials records and to adapt this to the particular purposes and needs of the medical school library.

The Jacobi Medical Library at The Mount Sinai Hospital is now expanding from the smaller function of the hospital library to the much larger and more responsible concern of the medical school library. The library has an integral role in medical education. It is, then, of utmost importance that the library service reflects modern standards of excellence in organization so that it may effectively fulfill its role as an information and learning resource center.

The medical library of The Mount Sinai Hospital is in the process of expanding the number of serial titles received from approximately 900 to 1800. Consequently, this is the ideal time to plan to mechanize the serials record, so that we will not incur later the additional costs of converting from a well established manual system.

This paper will deal with the costs of computerization and the ways in which computerization will improve work procedures and increase and expand the library's services. It will include a card layout showing how the information on a serials record card, used in a mechanized system, would be punched into IBM cards. The value of this plan is that it can be easily adapted to different library situations. Actually, the problems posed by serials subscriptions are similar for all libraries.

Subscribing to serials, which includes titles published in series as well as periodical publications, is a multifaceted operation. It is a job which requires many decisions. For monographs, once the decision to purchase is made there are no further important considerations. With serials, however, the librarian's responsibility extends beyond the initial subscription. At the time of the initial order we must decide whether to commence with the current issue or with the first issue of the current volume. Do we want back files immediately or in the future? Once the journal arrives we must solve the problem of binding. If an issue is lost, and out of print, we have to buy it from a supplier or vendor. If an issue is late in arriving we have to claim it from the publisher. Each year the decision to renew subscriptions must be made. Serials pose other problems for the librarian. They have changes in title more often than we care to count. This, together with the minor problems of changes in frequency, mergers and splits, places great demands on the librarian's attention and time. Because of the multitude of problems some sort of systematized solution is desirable.

In a library with approximately 1800 to 10,000 serials computer control is

feasible. This is the conclusion of a recently completed report by the Serials Computer Project of the library of the University of California at San Diego (1). According to the report, operating manpower costs appear to be comparable to those of manual systems.

No one institution has had a computerized system in operation sufficiently long for an exhaustive study on costs to be made. Hence, conclusions reached here are subject to revision.

It is obvious that processing serials and maintaining serial records are sufficiently independent areas of library activity to make possible a system which is not necessarily dependent upon other aspects of library operation. The repetitive character of much serials work admits of mechanization. The difficulty large libraries encounter in providing holdings and receipt information for their users suggests that by the use of data processing needed services can be provided at little or no additional cost. Also, the increase in services would justify the initial costs in manpower required for conversion to a computerized system.

The actual costs involved may be divided into three categories. First, the labor cost for serials processing and maintenance. Second, computer cost in terms of computer time and cost per unit of time. Third, the cost of computer programming and maintenance.

In examining labor costs there are a number of processes for which it is possible to make comparisons. Cataloging a new serial title or recataloging an old title is virtually the same process in a manual system as in one utilizing computers. The correct entry must be established and the library's holdings determined. Key punch is the only task requiring additional labor prior to converting the record to tape. The medical library at Washington University, St. Louis, required three hundred hours key punch time in developing their system for some 2500 titles (2). Studies on the time required to record periodicals using the computer-produced arrival file as against the manual system have shown that both procedures take approximately one minute per issue (3).

The cost of the computer in terms of time must also be considered. The total computer time cost cannot be compared directly with the costs of a manual system. Additional costs, however, are more than justified: information on holdings is more readily available to users; the claiming of missing issues and the bindery routine is simplified; and improved access to serials information to all departments of the library is provided. For example, the availability of a complete, up-to-date holdings list reduces the desk time spent in answering user's requests by at least several hours a day. Other savings are in equipment for storing records and, if serials are eliminated from card catalogs, in card reproduction, filing, and storage costs. Serials can be eliminated from the public catalog in a computerized system if there is available an up-to-date alphabetical and subject list of the library's holdings. It is difficult to estimate the cost of time involved in establishing the computer program. The University of Washington program used eleven hundred hours

for systems analysis and design, programming, report design, card layout, and documentation procedures (1). As programs are developed standardization should become possible. While libraries may need to adapt computer programs to fit their needs, the cost of installing a system should be much less when a number of libraries have successful systems in operation.

In the computerized system, as in any system, there are management costs. Ultimately, however, these should not be greater than in a traditional serials operation. Additional savings will be gained when bindery preparation forms and recording of bindery receipts are computerized. Subscription payment can also be incorporated into the program. Many services and work procedures could be expanded and made more efficient by a mechanized system.

The library can more easily make available lists of all issues received during the current month. In addition, lists of issues received daily could be made available. This is important in a scientific or medical library where the most frequently sought information is generally that which is most current and is available only in serial publications. Many library users are not able to come to the library on a certain day to determine if new titles of particular interest have been received. Daily acquisition lists could result from the method of checking journals into the library from pre-punched cards. The lists can be produced on an accounting machine, such as the IBM 407, or with a computer. At the end of this paper there will be a description of three methods of mechanization and approximate costs.

The mechanized system can be utilized in providing acquisition lists. Examples of two such lists are mentioned by Irwin Pizer in a report on the mechanization of the serials record at Washington University School of Medicine Library (4). His reason for planning these lists was threefold: to provide budget information; to facilitate the checking of vendor or supplier lists; to provide statistical data. The first list was arranged by supplier or vendor with the titles alphabetical in each group. The second was arranged alphabetically by title with the same information as the first list.

Other work procedures which would be greatly facilitated by computerization of the serials record are the receipt and the claiming of issues missing or not received. The computer can provide cards for all those issues expected within the month. When the issue arrives the pre-punched card for that issue is pulled from the file. At the end of each month the library has an instant record of those issues which it has not received. Human judgment is necessary in determining the length of time that should elapse before claim cards are dispatched.

The computer can be utilized for bindery notification. When the index to a volume is received the check-in card is punched. When the punch is sensed by the computer, the title is punched into a card which becomes the bindery notification for the serials assistant. One of the advantages of this use of cards is that they can be easily interfiled for future use if the bindery pickup is less frequent than the production of cards.

A service which is provided by The Jacobi Medical Library is the routing of

journals to department heads, administrators, supervisors and faculty members. This is a very time consuming operation presently handled by the serials assistant. The job could be greatly facilitated by a computerized serial record. One method would be to have coded into each serial record card the name of the person interested in examining each issue. The tables of contents could then be xeroxed when the issue arrives and sent to the interested party and the journal itself could be shelved.

The most valuable aspect of the mechanized system is the lists of the library's serials holdings which can be produced. These lists can be easily updated. They can range from very restricted one line per title lists to lists which have as much information for each item as a library catalog entry. As already indicated, the availability of subject lists would make it possible to remove serials from the card catalog. The subject headings for these lists can be adapted from such books as *Index Medicus* and *Ulrich's Periodicals Directory*.

In effect the possibilities of service are limited only by the ingenuity of the librarian-programmer and the extent of his source data. The serials system has the flexibility needed to rapidly fulfill requests for lists and information that in a traditional system would not be feasible.

The following is an example of an IBM card layout which forms an excellent foundation upon which to build. It can easily be adapted for use in any medium-sized or large reference library. This layout is based upon the description of the information to be punched into IBM cards from the serials record card, as given by Schultheiss et al (5) in their book on advanced data processing.

IBM card one

<i>Card Column</i>	<i>Information</i>
1 - 35	Short title: Generated by abbreviating the cover title with abbreviations used in <i>Index Medicus</i> or any other list of periodical abbreviations. Can also devise a code to represent journal titles.
36 - 38	Miscellaneous data: This code is intended for internal use. It is for such things as sort control.
39 - 43	Not used.
44 - 45	Routing list.
46 - 48	Shelving location.
49	Frequency.
50 - 61	Monthly frequency: This code should allow for such peculiarities as supplements.
62 - 69	Index number: A serials record card should be completed for each index received separately from the serial.
70	Status: Used to add or delete information or insert an original card into a master file.
71	Not used.
72	Card type: Always punched as card one.
73 - 80	Serial number: Each new serial should be assigned a number to reflect its alphabetical sequence. To derive a new number, locate the new

serial alphabetically and assign a number midway between the preceding and following number.

IBM card two

<i>Card Column</i>	<i>Information</i>
1 - 18	Partial library holdings: Beginning & ending volumes.
19 - 26	Subscription price: Or write gift, exch., etc.
27 - 32	Date current subscription started.
33 - 34	Subscription length in months.
35 - 40	Dealer code.
41 - 46	Color number: Assigned for binding.
47	No imprint indicator.
48	Binding class code.
49	Binding frequency.
50 - 61	Holding frequency code. Number punched in column for current month indicates how long to hold binding volume.
62	Sample back code, for binding information.
63	Index acquisitions code.
64	Index binding code.
65	Type of serial.
66 - 67	Year of last bound volume.
68 - 69	Plus or minus month number.
70	Status.
71	Not used.
72	Card type number (two).
73 - 80	Serial number: Same as other cards. Used for sort purposes.

IBM card three

<i>Card Column</i>	<i>Information</i>
1 - 60	Spine information for volume to be bound.
61 - 62	Day of week or month code: Refers to card one, column 49.
63 - 67	Estimated binding cost.
68 - 69	Not used.
70	Status.
71	Not used.
72	Card type number (three).
73 - 80	Serial number.

IBM card four

<i>Card Column</i>	<i>Information</i>
1 - 8	Purchase order number.
9 - 12	Fund number.
13 - 20	Bind with serial number. Refers to the index serial number if it is separate.
21 - 35	Appropriation number.
36 - 60	Appropriation description.
61 - 64	Estimated cost of each issue. Last actual cost becomes next estimate.
65 - 69	Not used.
70	Status.
71	Not used.
72	Card type number (four).
73 - 80	Serial number.

<i>Card Column</i>		<i>IBM card five</i>	<i>Information</i>
1	- 60		Binding title.
61	- 68		Not used.
69			Total lines.
70			Status.
71			Card number.
72			Card type number (five).
73	- 80		Serial number.

Following is a brief description of three methods of effecting a mechanized serials operation, including an estimate of machine costs (6). The first and least expensive method is to use tabulating or EAM (electrical accounting machinery) equipment: the IBM 407 or equivalent accounting machine for listing, counting and elementary report generating. Second, by using the IBM 82 sorter, the IBM 72 collator and the 026 key punch, one can effect a mechanized system. The sorter places cards in sequence and splits cards into groups according to certain "fields." The collator interfiles new cards. This method is straightforward but inflexible. The card manipulation is rigid and slow and is limited to the as-is use of data from the cards. The approximate cost of this setup is \$600 per month. Third, the fastest and most expensive method is the computer tape system. The cost of a computer tape operation is about \$3,000 per month. This setup utilizes the IBM 1401 (about 8K) with at least three tape drives, a card reader-punch and printer. The method enables one to keep a master file on tape. It is extremely high speed and provides a compact storage medium. In addition it has all the computer advantages of the second method.

Initial increased costs of mechanizing library serials record operations is justifiable in terms of the resultant more effective use of professional staff and library manpower resources. The library can improve services to its users and thus fulfill an important role in the field of medical education.

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Changing Pattern of Bacteremia

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The present report is concerned with the type and frequency of microorganisms isolated from the blood of patients at The Mount Sinai Hospital during 1966. Observations in this regard have been compared with those of a previous survey covering the three-year period from 1953 to 1955 inclusive (1), in order to ascertain whether or not variations have supervened with the passing of time. No significant modifications were instituted in the laboratory techniques employed or in the media utilized so that results obtained in both periods are directly comparable.

MATERIALS AND METHODS

The procedure employed for performing the blood cultures consisted of drawing approximately 17 ml of blood by venipuncture, after careful preparation of the skin as well as the diaphragm cover of each blood culture bottle with iodine and alcohol. Five ml of the aspirated blood was then injected into bottles containing approximately 100 ml of a) 1% yeast extract trypticase broth, b) 2% glucose broth and c) 0.005% paraminobenzoic acid broth. The remaining 2 ml was injected into a small bottle containing 20 ml of thioglycollate medium, for anaerobic culture. Penicillinase was added to neutralize potential growth inhibition of penicillin whenever the laboratory was apprised of the fact that the patient was receiving this antibiotic. Pour plates were not prepared as had been our previous routine since an analysis had failed to reveal any instances of the attainment of positive cultures in the solid pour plates where the liquid cultures had proven to be negative. All inoculated bottles were incubated in a lighted candle jar to obtain increased CO_2 concentration and, when a special CO_2 incubator became available about midyear, in a controlled atmosphere of 5% CO_2 . Each bottle was examined daily for growth and, in addition, smeared, stained and examined microscopically. Subcultures were made from each bottle into glucose broth, a liver tube for anaerobic culture and on blood, Endo and man-nite agar plates daily for the first four days. The cultures were observed for a minimum of two weeks before final report. Any organism or organisms found present were identified according to species on the basis of differential properties and reactions.

RESULTS

A resume of the 1966 blood culture findings, as compared to the yearly average of the 1953 to 1955 period, are contained in Table I. As in the earlier survey, all blood cultures performed on a patient, regardless of num-

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TABLE I

Analysis of Blood Cultures Performed in 1966 Compared to Yearly Average of 1953-1955

	1966	Average 1953-1955
Total blood cultures.....	2776	1786
Number positive cultures.....	353	115
Percent positive cultures.....	12.7	6.4
Multiple positive cultures.....	24	4
Two organisms.....	21	3
Three organisms.....	3	1
Per cent multiple positive cultures.....	6.8	3.5
Total number of organisms isolated.....	380	121

ber, were counted as a single culture in the tabulation of "Total Blood Cultures." If some or all of the blood cultures performed were found to harbor a particular organism, that strain was indicated as 1 "Positive Culture" and was tabulated only once among the "Total Number of Organisms Isolated." When two or more different organisms were recovered in one blood culture, it was counted as 1 "Positive Culture" and each of the recovered organisms was included among the "Total Number of Organisms Isolated." Confirmatory and repeat cultures, when positive, were not added to the total of "Positive Culture" or to the "Total Number of Organisms Isolated." Obvious contaminations or questionable isolates, as manifested by a lack of correlation with the presenting clinical picture or by their failure to be recovered on repeat culture, were not included among the positive blood isolates.

As may be noted from the table, more blood cultures were taken in 1966 than in the earlier period, with apparent justification since these yielded a far greater number of positive isolations. These amounted to 353 of 2776 cultures performed (12.7%) as compared to a yearly average of only 115 out of 1786 cultures (6.4%) earlier. The increase in the number of tests requested can be ascribed to some extent to the rise in the hospital census. The average bed capacity of the hospital excluding psychiatry and obstetrics, both of which have expanded greatly but contribute little to the number of blood cultures performed, was approximately 800 during 1953-1955 as compared to 1000 in 1966. The average number of patients admitted yearly during both periods, with the exclusion of the same services, was 261,000 in 1953-1955 and 322,000 in 1966.

It may also be seen from Table I that an increased number and proportion of multiple organism blood isolates is now being obtained. There were 24 such multiple isolations in 1966 or 6.8% of the total number of positive cultures as compared to only 4 or 3.5% in the earlier period. This experience apparently parallels that of other institutions. Hochstein et al (2) reported 52 multiple isolates out of 662 positive blood cultures (7.8%) at the NIH Clinical Center between 1954-1964, while Bodey et al (3) obtained 52 multiple blood isolates from 452 patients with acute leukemia (11.5%). Patients with leukemia, lymphoma, malignancy, etc., in whom the normal

defensive mechanism of the host is impaired, are most apt to manifest multiple organism blood invasions, and a significant proportion of patients from whom the multiple isolates were obtained in the present series, were so afflicted. Bacterial species most involved in these occurrences were found to be *Staphylococcus aureus*, *Escherichia coli*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa* and *Candida albicans*.

The varieties of microbial species implicated in the bacteremias of both periods and their relative frequencies are enumerated in Table II. These fall predominantly within three broad categories, namely a) Gram positive cocci, b) Gram negative enteric bacilli and c) Fungi.

Considering the Gram positive cocci group, although the number of strains of each species within this group were found to be much higher than in the earlier survey period, their relative proportion to the total number of organisms isolated was significantly less in 1966 (30%), than in the 1953-55 period (42.6%). Considering *Streptococcus viridans*, more strains of this species were isolated in 1966 but their proportion to the total number of organisms isolated now only represents 6.6% as compared to 15.1% previously. More strains of *S. aureus* and *Enterococcus* are also now being isolated but their relative proportions have remained relatively constant for both survey periods.

A noteworthy increase in the number of Gram negative enteric bacilli as well as of their relative frequency is apparent. This group now comprises 60.1% whereas they formerly represented only 48.7% of the total number of organisms isolated from the blood. Our experience in this regard is similar to that of institutions in different geographic locales, as is evident from recent reports (4-8). The absolute and relative increase in Gram negative bacteremias has been attributed to a number of factors. These include the generally advancing age of patients, who are now surviving to an age where malignancy and chronic urinary tract infections are more prevalent and these are undoubted causative factors. The more extensive use of indwelling intravenous and bladder catheters and the introduction and more widespread therapeutic utilization of radiotherapy, cytotoxic agents, steroids and antibiotics have also been contributory. The situation with respect to *A. aerogenes* is particularly noteworthy. One hundred fourteen strains or 30% of all organisms isolated from the blood were found to be members of this species as compared to 1953-1955 at which time they constituted only 14.6%. This significant rise is attributed to the generally increased antibiotic resistance of this species as well as to its frequent involvement in urinary tract infections from which blood stream invasions often stem.

Blood stream infections caused by fungi, particularly *Candida* species, have also increased markedly. Twenty-seven strains in this category were isolated in 1966 as compared to a previous yearly average of only one. This group of microorganisms comprises 7.0% of the organisms that are now being isolated from the blood, whereas formerly it accounted for only 0.9%. The same factors responsible for the increase in Gram negative bacillary sepsis are un-

TABLE II

Microorganisms Isolated from the Blood in 1966 Compared with Yearly Average of 1953-1955

Microorganism	1966		Average 1953-55	
	No.	% Total No. Organisms	No.	% Total No. Organisms
<i>Gram Positive Cocci:</i>				
Streptococcus viridans.....	25	6.6	18.3	15.1
Beta hemolytic streptococcus.....	11	2.9	2	1.7
Enterococcus.....	20	5.2	5	4.1
Gamma streptococcus.....	1	0.3	1.7	1.4
Diplococcus pneumoniae.....	13	3.4	5.7	4.7
Staphylococcus aureus.....	40	10.5	13.3	11.0
Staphylococcus albus.....	4	1.1	5.6	4.6
<i>Gram Negative Cocci:</i>				
Neisseria meningitidis.....	1	0.3	2.7	2.2
Neisseria flava.....	1	0.3	0	0.0
<i>Gram Positive Bacilli:</i>				
Clostridium perfringens.....	2	0.5	0.7	0.6
Listeria monocytogenes.....	1	0.3	0	0.0
Diphtheroid bacillus.....	1	0.3	1	0.8
Bacillus cereus.....	1	0.3	0	0.0
<i>Gram Negative Enteric Bacilli:</i>				
Escherichia coli.....	53	13.9	15.7	12.9
Aerobacter aerogenes.....	114	30.0	17.7	14.6
Klebsiella pneumoniae.....	1	0.3	1	0.8
B. proteus.....	15	3.9	8.3	6.9
B. proteus mirabilis.....	5	1.3	—	—
Pseudomonas aeruginosa.....	28	7.4	7	5.8
Salmonella.....	6	1.6	3.3	2.7
Shigella sonnei.....	1	0.3	0	0.0
Paracolon or atypical coli.....	4	1.1	3.7	3.0
Alkaligenes fecalis.....	1	0.3	2	1.7
Serratia marcescens.....	0	0.0	0.3	0.3
<i>Miscellaneous Gram Negative Bacilli:</i>				
Bacteroides.....	0	0.0	0.7	0.6
Hemophilus influenzae.....	1	0.3	3	2.5
Mima herellea.....	3	0.8	0	0.0
Brucella.....	0	0.0	0.7	0.6
Spirillum.....	0	0.0	0.3	0.3
<i>Fungi:</i>				
Candida albicans.....	13	3.4	0.7	0.6
Candida tropicalis.....	2	0.5	—	—
Candida parakrusei.....	2	0.5	—	—
Candida species.....	7	1.8	—	—
Cryptococcus neoformans.....	0	0.0	0.3	0.3
Histoplasma capsulatum.....	1	0.3	0	0.0
Saccharomyces.....	2	0.5	0	0.0

doubtedly operative with respect to the increase in *Candida* sepsis. The widespread use of antibiotics contributes particularly by altering the intrinsic protective bacterial flora of the body.

Considering the less common blood isolates, both *Neisseria meningitidis* and *Hemophilus influenzae septicemia* were found to occur less frequently. The recovery of three *Mima herellea* strains from the blood in 1966 contrasts with their complete absence in the earlier three-year period. A greater awareness of the pathogenic potential of this species at the present time as well as increased knowledge about their laboratory differential diagnostic characteristics may well have been responsible for the increased number of recoveries of their relatively newly described group of microorganisms.

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Unusual Problems in Surgery

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CASE NO. 10

Presacrococcygeal Cyst

The presacrococcygeal or retrorectal zone is that region bounded by the lower part of the rectum anteriorly, the sacrum and coccyx posteriorly, and the iliac vessels and ureters superiorly and laterally (1). The space contains loose areolar tissue which is continuous with that of the retroperitoneal space above the pelvis.

This zone is the site of bizarre tumors; inflammatory, malignant and developmental (1, 2). A presacrococcygeal cyst is a retrorectal tumor comprised of either dermoid, epidermoid, or teratomatous elements, whether or not there are fistulous communications with the rectum, anus, or other perianal areas. Primary cysts of this region are extremely rare as demonstrated in a report from the Mayo Clinic (3) in which only 38 cases were encountered in routine proctoscopic examinations of 20,851 cases.

After the publication of Middeldorpf's article in 1885 (4), in which he reported a presacral teratoma in a one-year-old child, most extra rectal tumors occurring on the posterior rectal wall have been called Middeldorpf tumors. However, in an exact

sense, only teratomas in this region should be so designated. Several authors state that most presacrococcygeal cysts are teratomas (3, 5).

The presacral area is the site, in the embryo, of fusion of: 1. central nervous system, 2. skeletal axis, 3. segmental musculature and 4. postanal gut. With this complicated development, there is considerable disagreement as to the exact derivation of dermoids and teratomas. It is generally accepted that they arise from cell nests of the neuroenteric canal, postanal gut, proctodeal membrane, anal plate, or from the spinal cord extension from the third sacral segment to the tip of the coccyx (6).

A teratoma (7) is a neoplasm which has the potential of both benign and malignant growth. Derivatives from all three germ layers are observed, and they distinguish the tumor from dermoid cysts in which only ectodermal derivatives are found. Teratomas may be solid, cystic or both and contain skin, bone, cartilage, visceral organs, adipose tissue, etc. The cysts may contain sebum, mucoid secretions or cerebrospinal fluid. Histologically, the teratoma may be embryonic, mature or immature. The fully mature tissues of benign teratomas closely resemble their normal counterparts. Another type may become malignant, metastasize widely via lymphatics and blood vessels, and lead to rapid death of the patient.

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Because they may become infected or rarely undergo malignant degeneration, they should be surgically excised. The following is a case report of a presacrocoecal teratoma treated in a patient at The Mount Sinai Hospital.

CASE REPORT. The patient was a 24-year-old woman with chief complaint of difficulty and pain upon introduction of a vaginal tampon. The problem was first noted several months prior to admission. As the insertion of the tampon became more difficult, the patient sought consultation with her gynecologist, who, following examination, referred her for surgery.

There was no history of change in bowel habits or of problems with micturition. She had not noticed any abdominal mass or had abdominal pain. Her menses were regular. Past history was not contributory.

Physical examination revealed a well-developed, well-nourished, white woman in no acute distress. Vital signs were normal and positive physical findings were confined to the abdomen and pelvis. The abdomen was soft. The liver, spleen, and kidneys were not palpable. A soft, slightly tender, cystic mass was felt occupying the lower part of the abdomen extending down into the pelvis with its highest point in the midline, four fingerbreadths above the symphysis pubis. Rectopelvic examination also revealed the slightly tender, soft mass displacing the rectum anteriorly. Neurologic examination was within normal limits. Laboratory studies disclosed the following values: hemoglobin, 14.4 gm/100 cc; white blood cell count, 9,400, differential normal; blood urea nitrogen, 16 mg/100 cc; fasting blood sugar, 90 mg/100 cc; urinalysis normal; x-ray examinations: chest, normal; barium enema: rectum was markedly displaced anteriorly and to the right by a large soft tissue mass posterior to the rectum which appeared intrinsically normal as did the remainder of the colon. Intra-

venous pyelography demonstrated a normal collecting system bilaterally, some dilatation of both ureters, with the bladder displaced upwards and to the left. The bladder revealed no intrinsic abnormality. Tomographic examination of the sacrum in the lateral view failed to reveal any area of erosion anteriorly or widening of the spinal canal. There were no soft tissue calcifications seen.

HOSPITAL COURSE. Following preoperative preparation, the patient was taken to surgery. Ureteral catheters were passed just prior to laparotomy. The abdomen was entered through a lower transverse incision. A large retroperitoneal cystic mass was dissected away from its retrorectal position with care being taken not to injure the ureters which were in close approximation throughout. By mobilizing the rectum and presacral fascia, the tumor was dissected down to the pelvic floor. During the course of dissection, the cyst ruptured, and thick yellow-white sebaceous material was noted. Multiple frozen section biopsies revealed the nonmalignant nature of the tumor. Within the main cyst, there were seen several smaller cysts within cysts. The mass was dissected down to its coccygeal attachments and removed. Drains were placed in the presacral region and brought out through the perineum and the abdomen closed.

Pathological examination of the tumor revealed a benign cystic teratoma of the sacrocoecal region. No immature tissue elements were found.

The postoperative course was unremarkable and followup examinations have revealed no evidence of recurrence.

DISCUSSION. Congenital tumors such as teratomas usually cause symptoms from pressure or infection. As the tumors increase in size, pressure may cause bladder symptoms, constipation, rectal pains, pelvic discomfort, and low back pain. The symptoms can therefore mimic those of many other

pelvic-rectal masses, including pregnancy. These tumors do not cause neurological symptoms (6). Infection usually results from rupture into the rectum or perineum. It is important to recognize that these tumors may give rise to perineal sinus tracts at the tip of coccyx or along the coccyx or lower sacrum. In one series (6), five of eleven patients with congenital tumors in this region had a mistaken diagnosis of either pilonidal sinus or anorectal fistula.

Digital examination of the rectum will almost always reveal the tumor mass between the sacrum and rectum. The presence of teeth on x-ray examination will frequently establish the diagnosis of teratoma.

The differential diagnosis of mass in the presacrococcygeal area includes a large variety of congenital anomalies, osseous, neurogenic, inflammatory, and miscellaneous tumors (1, 2). In two reported series (6, 8), chordomas represented the other major tumor found in this region.

The treatment of sacrococcygeal cysts is surgical. Smaller tumors can be approached with a dorsal lower midline or parasacrococcygeal incision (3, 6). The coccyx can be removed for better exposure. If the tumor is too large to be excised by this approach, abdominal incision is necessary. The passage of ureteral catheters, though not guaranteeing the absence of damage to the ureters, can at least help define these often closely approximated structures.

Where there is an infected cyst with a draining sinus, treatment involves tracing the sinus to the infected cyst and attempting to excise all involved tissue. Where dissection is difficult,

and anal-rectal damage can occur, certain authors (3) suggest simple marsupialization of the cyst into the rectum.

The results of surgical removal of teratomas are excellent (3), if the lesions can be completely excised. Watchful observation and irradiation have no place in the therapy of these tumors (5).

SUMMARY. A case of presacrococcygeal cyst is presented. These tumors are comparatively rare but when a cystic tumor occurs in this region, it will most likely be a teratoma. Treatment is surgical to prevent malignant degeneration or infection.

—*Lewis Burrows*

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CASE NO. 11

Meconium Peritonitis

Meconium peritonitis is a chemical inflammation produced by the leakage of meconium into the peritoneal cavity of a fetus or newborn infant. The condition is uncommon, and is associated with an extremely high mortality rate (3, 7, 8, 11, 15). The entity was first described by Morgagni in 1761. Since Agarty's description of the first successful operative case in 1943 (1), approximately 75 additional survivals have been reported in the English literature (3).

The Pediatric Surgical Service of Elnhurst General Hospital recently encountered and successfully treated a case of meconium peritonitis which was due to a perforation of the small intestine proximal to an area of atresia and duplication of the ileum.

CASE REPORT. On September 22, 1966 a 2630 gm female infant was delivered during an episode of fetal distress. The fetal heart rate was 200/min and the amniotic fluid was meconium stained. Following birth, the infant was apneic for two minutes. An endotracheal tube was inserted and meconium was aspirated from the trachea as well as from the stomach. The baby's Apgar score was 3. Four hours after delivery the child was seen by the Surgical Service because of abdominal distention and vomiting of bile stained fluid. Physical examination revealed a pale infant with peripheral cyanosis and a feeble cry who appeared to be in acute distress. The pulse rate was 180/min, the respirations were 48/min, and the rectal temperature was 94.6° F. The conjunctivae and mucous membranes were pale. Respirations were grunting and although both lungs aerated well, supraclavicular and intercostal retractions were seen. Engorged veins were prominent over the markedly distended ab-

domen. No intraabdominal masses or organs were palpable. The rectum was of narrow caliber and contained greyish mucoid material. Laboratory studies revealed the following values: hemoglobin, 11.6 gm/100 cc; hematocrit, 37%; white blood cell count, 33,000/cu mm, with 58% polymorphonuclear leukocytes, 31 lymphocytes and 11% monocytes. The total bilirubin was 1.9 mg/100 cc (direct 0.2 mg/100 cc). X-ray films taken two hours after birth showed a generalized haze over the entire abdomen. Films taken four hours after birth showed some air containing loops of jejunum in the left mid-abdomen. There was no progression of air into the ileum or large bowel. No definite calcifications were seen within the abdomen (Fig 1). The chest roentgenogram was unremarkable.

A nasogastric tube was inserted and 50 cc of bile stained fluid was aspirated from the stomach. A paracentesis was performed in the lower abdomen using an Intracath.* Black-green liquid meconium was obtained (Fig 2), and the diagnosis of intrauterine perforation of the intestinal tract was therefore established. Approximately 150 cc of this material was slowly withdrawn.

The infant's general condition was extremely poor. Preoperative preparation was aimed at treatment of shock with intravenous fluids and blood, restoration of the infant's body temperature, and removal of the intraperitoneal fluid and intestinal gas to allow better expansion of the lungs. The baby was placed in an Isolette in an atmosphere of oxygen and high humidity. Antibiotics were administered parentally (kanamycin and sodium penicillin). The baby received 100 cc of 0.5 N saline and 50 cc of whole blood intravenously. Vitamin K was given. Her color gradually improved, peripheral cyanosis disappeared and the child voided. Surgery was performed when the infant was nine hours old. Anesthesia consisted of 8 cc of 0.5% Xylocaine which was injected locally. Dur-

* Intracath® C. R. Bard, Inc., Murray Hill, N.J.



Case No. 11, Fig. 1. Plain film of the abdomen at four hours of age. Note diffuse haze over the abdomen and lack of intestinal air beyond the jejunum.

ing surgery, oxygen was administered by means of an endotracheal tube. A heating blanket was used to maintain the infant's temperature, and the heart

rate was monitored on a cardioscope. Exploration was carried out through a transverse supraumbilical incision. The peritoneal cavity contained a large



Case No. 11, Fig. 2. Infant after removal of 100 cc of intraperitoneal meconium with an Intracath and syringe. Dilated veins are visible on the abdominal wall.

amount of liquid meconium. A plastic exudate was present over the entire peritoneal cavity, and all bowel loops were matted together. A large patent perforation was present in the proximal ileum which was markedly dilated and congested. Seventeen centimeters distal to the perforation was an area of atresia of the ileum, adjacent to which was a 1 x 1.5 cm sausage shaped mass (Fig 3). The small bowel distal to the obstruction was of narrow caliber, but otherwise appeared to be normal. The visible portions of the colon appeared to be normal. In order to ascertain the patency of the distal ileum, normal saline was gently injected through a 25 gauge needle into the lumen of the bowel. This step was essential because of the possibility of multiple areas of atresia, as well as the fact that it dilates the distal bowel and facilitates the anastomosis. Approximately 30 cm of ileum was resected and intestinal continuity was restored by means of a

two layer end-to-end anastomosis using interrupted 5-0 silk sutures.

A Stamm tube gastrostomy was performed using a small mushroom catheter which was brought out through stab wound in the left upper quadrant of the abdomen. The abdomen was not drained. One hundred cubic centimeters of blood was given during surgery.

PATHOLOGY. The resected specimen consisted of 26 cm of ileum (Fig 4). The distal portion of the bowel was obstructed by an area of atresia measuring 2.5 cm in length. Seventeen centimeters above the obstruction there was an area of gangrene and perforation of the bowel. The intestinal wall was hemorrhagic and necrotic. Sections from the completely atretic segment showed that the lumen was replaced by fibrous tissues. Adjacent to the atretic ileum was a small duplication of bowel, microscopic examination of which revealed



Case No. 11, Fig. 3. Operative photograph. Forceps points to duplication distal to dilated ileum (A).

two lumena partially lined by intestinal mucosa. A thick muscle coat surrounded one lumen while the other was surrounded by thin muscle layer. The findings were consistent with atresia and duplication of the ileum with proximal dilatation, gangrene, perforation and peritonitis.

In the postoperative period intravenous fluids were carefully regulated, using skin turgor, body weight, urinary output, and pulse rate as guidelines. The gastrostomy tube was allowed to drain by gravity and the drainage was replaced with equal amounts of saline intravenously. On the fourth postoperative day, intestinal peristalsis had returned, and the following day gastrostomy feedings of glucose water were begun. Feedings were gradually increased in volume, and oral feedings were soon tolerated. On the 13th postoperative day the gastrostomy tube was removed. The baby was discharged home on the 24th postop-

erative day, at which time she weighed 2720 grams. When last examined at 10 months of age, the baby weighed 17 lbs and was doing well.

DISCUSSION. Meconium is a sterile mixture of bile, epithelial cells, amniotic fluid, pancreatic, gastric and intestinal secretions which is normally present in the intestinal tract of developing fetuses. When meconium escapes into the peritoneal cavity, a chemical peritonitis is produced. This has been shown in experimental animals by Rubovits, Taft and Neuwelt (14).

Meconium peritonitis may occur as early as the fifth month of fetal life or as late as several days after birth. The actual perforation may occur during labor or shortly afterwards as a result of increased peristalsis and the mechanical forces of labor itself (5).



Case No. 11, Fig. 4. Surgical specimen. Note atretic segment, A; Duplication, B; Dilated ileum, C; and Perforation, D.

ETIOLOGY. The majority of cases are associated with some form of intestinal obstruction (3, 15), the most common being meconium ileus (mucoviscidosis) and intestinal atresia or stenosis (3, 7, 15). Among the rarer causes of obstruction causing meconium peritonitis are volvulus (8), intestinal duplication (3), internal hernia, peritoneal bands (15), and intussusception (13). Perforation of a Meckel's diverticulum has been reported (9). Occasionally, no cause for the perforation can be found (4, 8).

The mechanism of perforating depends upon the underlying lesion. Active peristalsis above an obstructing lesion of the intestine produces distention of the bowel with subsequent ischemic necrosis and perforation. Volvulus comprises the intestinal blood

supply, resulting in necrosis and perforation. Meconium peritonitis due to inspissated meconium generally is associated with cystic fibrosis of the pancreas. Because of the absence of pancreatic secretion, meconium within the bowel becomes putty-like and adherent to the bowel wall and cannot be propelled along the gastrointestinal tract. Perforation of the bowel may then occur proximal to the obstruction.

Occasionally, an intrapartum perforation will seal off at the time of birth (3, 15). If the perforation remains open without prompt surgical treatment massive pneumoperitoneum and bacterial peritonitis may supervene.

DIAGNOSIS. Many of these infants are

born dead or die soon after birth (11). Those who survive present the picture of intestinal obstruction, the symptoms depending upon the level of obstruction. Bilious vomiting, abdominal distention and abnormalities in meconium evacuation are almost constant findings (3). Respiratory distress is common (3) and is usually the result of abdominal distention. X-ray studies are of value if small intestinal obstruction, pneumoperitoneum, or intraperitoneal calcifications are demonstrated (15). In a recent series of 99 cases of neonatal peritonitis (3), plain films of the abdomen were sufficient to indicate the need for operative intervention in almost all instances. Approximately 30% of films showed varying amounts of calcific flecks in the peritoneal cavity, diagnostic of meconium peritonitis. Needle aspiration of the peritoneal cavity may occasionally be helpful. In our case we were able to make a definite diagnosis following paracentesis.

MANAGEMENT. The essential elements in the management of these patients is adequate preoperative preparation and prompt surgical intervention. Shock, hypothermia, electrolyte disturbances, and dehydration must be corrected. Infants in a hypothermic state do not withstand surgery as well as normothermic babies. Nasogastric suction, adequate oxygenation, intravenous fluids, and antibiotics should be administered before the infant is moved for x-ray or any other investigation.

The surgical management depends upon the underlying pathology. The majority of patients require a resection of the dilated, poorly functioning bowel proximal to an obstruction, as well as the removal of badly matted

bowel and areas of atresia, stenosis or necrosis (3). Resection of all of the involved bowel including the dilated proximal intestine is essential. It has been shown by Benson et al (2) that, if the ileocecal valve is retained, all but 30 cm of small intestine can be removed from the neonate without causing malnutrition. Following this, one of several operations may be performed. End-to-end anastomosis may be performed when inspissated meconium due to mucoviscidosis is not a problem. Gross (3, 6, 12) advocates the use of a Mikulicz double barrel enterostomy with delayed closure. In cases of meconium ileus, pancreatin can be instilled into the distal limb. Although serious fluid and electrolyte disturbances are said to occur in infants with enterostomies, Gross has seldom encountered this complication. Bishop and Koop (4) advocate resection with end to side ileo-ileostomy and exteriorization of the end of distal loop. The obstruction is temporarily relieved by the ileostomy and pancreatic enzymes can then be instilled in the distal ileum to soften the meconium. In Holschlaw's series (10) the Bishop-Koop operation offered the most favorable result in meconium ileus. Occurrence of postoperative electrolyte problems was minimal.

The risk of aspiration pneumonia which is a major cause of death in these patients, may be reduced by the use of a tube gastrostomy.

Meticulous care in the postoperative management of these infants is essential.

SUMMARY. A case of meconium peritonitis due to atresia and duplication of the ileum is reported, and the entity of meconium peritonitis is reviewed.

Early diagnosis, careful pre- and post-operative management and prompt surgical intervention aided in this infant's survival.

—*Mahmood Naqvi, and
A. Robert Beck*

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CLINICO-PATHOLOGICAL CONFERENCE

Liver Disease In An Alcoholic Male

Edited by

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A 61 year old man entered the Mount Sinai Hospital because of fatigue, anorexia, diarrhea and abdominal cramps of six months duration.

Six months prior to entry he noted increasing weakness, anorexia, and loss of weight. On admission to another hospital the liver was palpated four fingerbreadths below the right costal margin. The hemoglobin was 12.7 gm/100 cc; the white blood count 8,850/cu mm and the erythrocyte sedimentation rate (ESR) 118 mm/hr. The blood urea nitrogen (BUN) was 32 mg/100 cc; total serum bilirubin 1.3 mg/100 cc; alkaline phosphatase activity 6.5 Bodansky units and serum glutamic oxalacetic transaminase 50 units. The serum albumin was 4.1 gm/100 cc and the globulin value 3.5 gm/100 cc. The prothrombin time was 15 seconds, and a serologic test for syphilis was nonreactive. One month later, because of persistent symptoms, an exploratory laparotomy was performed. At operation, the liver was said to be nodular and a surgical biopsy specimen of the liver was reported as showing early cirrhosis. Following discharge the patient noted further loss of weight, weakness, and he developed non-bloody diarrhea. Three weeks prior to admission he fell and injured his right side.

The patient consumed large quantities of alcohol for many years. He denied recent alcohol intake or exposure to toxins.

He appeared obtunded, malnourished and dehydrated. The blood pressure was 110/75, pulse rate 80 beats per minute, respiration 18 per minute and temperature 98.8°F. The sclerae were icteric and the conjunctivae were pale. Two small spider angiomas were present on the chest wall. The heart and lungs were normal. A mass was palpated in the right upper quadrant over which a systolic bruit was heard. The spleen was not felt. No clubbing, cyanosis, ascites or peripheral edema was present. Neurologic examination revealed an organic mental syndrome.

The hemoglobin was 10.6 gm/100 cc; the white cell count 7,750/cu mm with a normal differential count; the platelet count 454,000/cu mm and the ESR 106 mm/hr. The urine specific gravity was 1.015. There was slight proteinuria and a trace of Bence Jones protein was detected by the Jacobson method. The urinary sediment was normal and tests for heavy metals were negative. The BUN was 37 mg/100 cc; serum creatinine 3.0 mg/100 cc; fasting blood sugar 94 mg/100 cc and total serum cholesterol 290 mg/100 cc. The total serum bilirubin was 0.4 mg/100 cc, alkaline phosphatase activity 15.6 King-Armstrong units and serum glutamic oxalacetic transaminase 33 units. The serum sodium

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was 144 mEq/liter. The serum albumin level was 2.8 gm/100 cc and globulin 6.2 gm/100 cc. Electrophoresis of the serum showed a diffuse elevation of the gamma globulin fraction. The serum calcium was 13.1 mg/100 cc and the phosphorus 4.8 mg/100 cc. Bleeding, clotting and prothrombin time was normal. A stool specimen was guaiac positive. An x-ray examination of the chest on admission showed fractures of the fifth through eighth right ribs, posteriorly. An electrocardiogram was normal.

The patient improved with oral feedings, intravenous fluid and vitamin therapy but appeared lethargic and was occasionally incoherent. A spinal fluid examination was normal. The bone marrow was hypercellular with increased erythroid and granulocytic activity. No abnormal cells were present. On the 12th hospital day his temperature rose to 102°F. and he became hypotensive and unresponsive. The white blood count was 13,700 per cu mm with a shift to the left. Therapy with penicillin, streptomycin and corticosteroid was begun. A throat culture grew *Staphylococcus aureus* which was coagulase positive. Wyamine was required to maintain the blood pressure and Staphcillin and isoniazid were added. Forty-eight hours later he was afebrile and the blood pressure was maintained without vasopressors. He remained semicomatose. The BUN was 54 mg/100 cc; serum sodium 143 mEq/liter; potassium 8.0 mEq/liter; chloride 108 mEq/liter and carbon dioxide 13 mEq/liter. The serum calcium was 13.1 mg/100 cc and phosphorus 4.7 mg/100 cc. An x-ray examination of the chest revealed a nodular density in the right lower lung field and lytic lesions in the thoracic vertebrae. X-ray films of the hands were normal. The previous surgical biopsy of the liver was reviewed and was reported as showing inflammation of the portal tracts, steatosis, and no evidence of cirrhosis. The physical examination of the abdomen remained unchanged. *Salmonella derby* was isolated from the stool and Chloromycetin therapy was begun. On the 21st hospital day, the BUN was 130 mg/100 cc and serum potassium 9.4 mg/100 cc. Kayexalate and Alkeran therapy were given. The following day he became hypotensive and died.

*Dr. Alexander B. Gutman:** This 61 year old man came to the Mount Sinai Hospital because of fatigue, anorexia, diarrhea and abdominal cramps.

Six months before, at another hospital, his liver was palpated four finger-breadths below the right costal margin and the erythrocyte sedimentation rate was 118 millimeters per hour. Worth noting, however, was the elevated blood urea nitrogen, the serum bilirubin and serum alkaline phosphatase activity. The serum proteins were normal and the physical examination was not revealing. One month later an exploratory laparotomy was performed. Apparently his physician suspected a tumor because of the loss of weight and weakness. At operation, the liver was described as nodular and a surgical biopsy specimen of the liver was reported as early cirrhosis. However, subsequent examination of the liver biopsy specimen questioned this diagnosis. The surgery did not ameliorate his symptoms, and following discharge he noted further loss of weight, weakness and he developed nonbloody diarrhea.

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Three weeks prior to admission to this hospital, he fell. Since he was an alcoholic, he may have been intoxicated. In any case he injured his right side and we are told later that he fractured a number of ribs.

On admission, he was malnourished and dehydrated. The cause of his obtunded state was not apparent from the history and physical findings. The vital signs were normal and he was afebrile. The sclerae were described as icteric although the serum bilirubin was normal. He probably had the discolored sclerae seen so often in chronic alcoholics. Of significance were two small spider angiomas present on the chest wall, which are usually associated with cirrhosis of the liver or acute hepatitis. A mass was palpated in the right upper quadrant over which a systolic bruit was heard. We all attach a great deal of significance to systolic bruits since they generally signify vascular tumors. It is not clear whether this bruit was heard over the liver or posteriorly where bruits of renal tumors are usually heard. I presume the bruit was anterior and over the liver. The spleen was not felt and apparently there was no evidence of collateral circulation. There was no clubbing, cyanosis, ascites or peripheral edema. Most prominent was his confused state or, in neurologic terms, organic mental syndrome. Laboratory studies revealed a mild anemia, a normal white blood cell count and differential, and a normal platelet count. The erythrocyte sedimentation rate was 106 millimeters per hour. The urine was normal except for slight proteinuria. A trace of Bence Jones protein was detected by the Jacobson method. However, one should be suspicious of such a report, since it is very difficult to detect Bence Jones protein in trace amounts unless electrophoretic studies are performed. The urinary sediment was normal. Tests for heavy metals were negative. Probably, they were performed suspecting lead poisoning related to drinking home-made alcohol which may be heavily contaminated with lead.

The blood urea nitrogen was 37 milligrams per cent and the serum creatinine 3 milligrams per cent. The blood sugar level was normal, and in spite of an enlarged liver containing a mass, the serum bilirubin was 0.4 milligrams per cent.

Noteworthy was the normal serum alkaline phosphatase and serum glutamic oxalacetic acid activity. Except for an elevated serum potassium level related to renal insufficiency and perhaps an early indication of acidosis, the serum electrolytes (sodium and chloride) were normal but the CO_2 was 17.5 milliequivalents per liter. The serum albumin level was reduced and the globulin was markedly increased due to a diffused increase of all gamma globulin fractions. He presented a puzzling clinical state. He was not uremic, nor did he show signs of hepatic insufficiency, yet he was obtunded. Bleeding, clotting and prothrombin time were all normal, indicative of preserved hepatic function.

A stool specimen was guaiac positive but there was no evidence of gross bleeding. An x-ray examination of the chest showed fractures of the fifth through eighth right ribs, posteriorly, presumably related to trauma. Whether the trauma was sufficient to account for the rib fractures or whether we must

assume neoplastic involvement of the bones which predisposed to the fracture, I am unable to state. An electrocardiogram was normal.

We have learned through experience that unexplained organic mental syndromes may be due to abnormal serum calcium levels. In this instance the serum calcium level was 13.1 milligrams per cent and the phosphorus 4.8 milligrams per cent. Presumably, his sensorial difficulties were related to hypercalcemia.

He was treated with oral feedings and large amounts of intravenous fluids, a simple and effective way of managing hypercalcemia in many cases. A spinal fluid examination was normal. A bone marrow determination performed to exclude multiple myeloma was hypercellular and there was both increased erythrocytic and granulocytic activity but no abnormal cells. On the twelfth day, he developed a fever, became hypotensive and unresponsive. The white blood count rose to 13,700 per cu mm with a shift to the left. Apparently he developed an infection and therapy with penicillin, streptomycin and corticosteroids was begun, suspecting a gram negative infection. However, *Staphylococcus aureus* which was coagulase-positive was cultured from his throat. The blood pressure was restored with Wyamine. Staphicillin and isoniazid were added to the therapeutic regimen. Whatever agents were responsible, he was afebrile within 48 hours and his blood pressure was maintained without vasopressors. However, he remained semicomatose. The blood urea nitrogen level rose to 54 milligrams per cent, the serum potassium to 8 milliequivalents per liter and the carbon dioxide fell to 13 milliequivalents per liter. In other words, he developed azotemia and renal acidosis. His serum calcium level was again 13.1 milligrams per cent and the serum phosphorus was elevated consistent with the elevated blood urea nitrogen. An x-ray examination of the chest revealed a nodular density in the right lower lung field, lytic lesions in the thoracic vertebrae and mild demineralization of some bones. Review of the surgical biopsy of the liver performed six months earlier showed a cellular infiltration in the portal tracts and fat. I presume the portal tracts were cellular as well as fibrotic but the liver was not cirrhotic. In fact, clinically, there was no evidence of cirrhosis since neither superficial venous collateral channels nor esophageal varices were found, and the spleen was only slightly enlarged. Neither parenchymal damage, jaundice nor obstruction of the portal circulation and hypertension was present. The physical examination of the abdomen remained unchanged. The liver was not enlarging and the mass within the liver persisted. The azotemia progressed and on the 21st hospital day, the blood urea level nitrogen was 130 milligrams per cent and the serum potassium 9.4 milligrams per cent. He was treated with Kayexalate to lower the serum potassium. Alkeran therapy was also instituted. The following day he became hypotensive and expired. As I indicated, perhaps the most striking aspect of this man's illness was the disproportionate clouding of the sensorium, the only explanation for which was hypercalcemia. He was not in hepatic coma, and he became obtunded long before he was overtly uremic.

Therefore, we might consider the various causes of hypercalcemia. In primary hyperparathyroidism without renal involvement, the serum phosphorus is reduced. His phosphorus was always at the upper limit of normal or slightly elevated. He did have renal disease, but initially when hypercalcemia was first noted, the degree of renal insufficiency was not very marked and I would have expected a lower serum inorganic phosphate. Moreover, he did not have generalized skeletal demineralization as in the chronic forms of primary hyperparathyroidism. Roentgenograms of the hands, for example, were normal, and there was no history of urinary calculi.

Since he did have some form of renal disease, one should also consider secondary hyperparathyroidism. His renal insufficiency was too brief and mild, in my opinion, to explain the hypercalcemia. Might he have had multiple myeloma? He had a trace of Bence Jones protein in the urine and a marked hypergammaglobulinemia but without a homogeneous spike. The diffuse elevation is more consistent with hepatic disease than with myeloma. Progressive renal insufficiency occurs in multiple myeloma due to precipitation, or excessive reabsorption of proteins by the tubules. However, the bone marrow examination failed to disclose an increase in plasma cells. He might have had a hypernephroma. He had a mass in the flank or in the right upper quadrant and it is difficult at times to make this differentiation.

Hypernephromas are very vascular tumors and are frequently associated with bruits. It would be surprising to have a hypernephroma of this size without bleeding into the urine, although hematuria occurs later in the course of hypernephroma than is generally appreciated. Anemia is not a common feature and he did not have polycythemia. There was no evidence of extensive metastatic involvement of the liver which you might expect with hypernephroma if he had extensive skeletal metastases. The serum alkaline phosphatase activity in fact was not elevated. I cannot rule out hypernephroma but would not consider it my first choice. The nodule in the lung suggests the possibility of bronchogenic carcinoma. He had no pulmonary symptoms or clubbing of the fingers, although a small bronchogenic carcinoma may metastasize extensively to the skeleton. Having considered these possibilities I must also include hepatoma, since he was an alcoholic with evidence of chronic liver disease who began to deteriorate. A primary hepatoma would account for the enlargement of the liver and the systolic bruit. Could we account for the hypercalcemia which I presume was due to extensive skeletal metastases on the basis of a hepatoma of the liver? Tumors of the liver metastasize, although this is not one of their major characteristics. They usually grow by extension and metastasize within the liver and to regional nodes. However, about three per cent of patients with hepatoma develop skeletal metastasis. Of interest is that the liver cells continue to secrete bilirubin and so the metastases have a green color. In this setting, hepatoma of the liver should be seriously considered, although I do not remember a case with such rapidly progressive skeletal metastases as to result in marked hypercalcemia. I also would have expected that the serum alkaline phosphatase activity would be

increased. A rise in alkaline phosphatase activity is often the first manifestation of secondary metastatic involvement of the liver. If the hepatoma were located near the fundus or left lobe of the liver and did not compromise major hepatic vessels and ducts, it might not affect the serum alkaline phosphatase activity. Progressive renal insufficiency is often associated with hepatic disease, but usually the hepatic disease is more pronounced. However, the hypercalcemia was at least, in part, responsible for the progressive renal insufficiency also seen with hyperparathyroidism and with sarcoidosis. Therefore, as my first choice, I think this patient had primary tumor of the liver with extensive metastases involving the skeleton, the lungs, the liver and lymph nodes, and this was responsible for the hypercalcemia and the resulting renal insufficiency.

*Dr. Hans Popper:** Thank you Dr. Gutman. At the autopsy, the lungs showed extensive emphysema. In the apices of the lungs was an acute bronchopneumonia which explained the terminal event of fever, leukocytosis and shock. The heart was of normal size. The myocardium showed increased fibrous tissue and some slight hypertrophy of the myocardial fibers. The kidneys were of normal size and showed a moderately advanced nephrosclerosis with a milder degree of arteriosclerosis. In the bones examined, there were no metastatic lesions and the marrow was moderately cellular without any significant plasmacytosis. The testicles were more atrophic than expected for his age and was probably related to alcoholic abuse or liver disease, or both. The pancreas was entirely normal. There were hemorrhagic lesions in the large and small intestines, no doubt uremic in origin. In addition, the small intestine was hyperemic suggesting portal hypertension or at least mesenteric venous outflow block. Since there was no evidence of an acute or chronic inflammation, I cannot explain the diarrhea. In the esophagus, we found a few small dilated vessels also indicative of an outflow block.

The right adrenal weighed 270 grams and the left 55 grams, and was the site of an anaplastic carcinoma (Fig 1). Although we were unable to find adrenal tissue, I cannot exclude active adrenal tissue buried within the mass.

The lymph nodes around the pancreas also contained anaplastic carcinoma. The spleen was slightly larger than normal. Histologically, there was atrophy of the follicles, reticuloendothelial hyperplasia, and fibrosis consistent with portal hypertension. Our main interest was in the liver. The surface was smooth, but puckered in areas which frequently leads the surgeon to misdiagnose cirrhosis at operation. The puckering is probably a peculiarity of Glisson's capsule. On section, there was no evidence of cirrhosis. However, several tumor masses were scattered throughout the substance of the liver (Fig 2). The tumor was extremely anaplastic in most places. Many veins were invaded by and contained tumor tissue which extended into the portal vein (Fig 3).

Small metastatic nodules with invasion of the vessels were found in the lungs. In some areas within the liver, the tumor had a characteristic trabecular ar-

* Pathologist-in-Chief, The Mount Sinai Hospital, New York City.

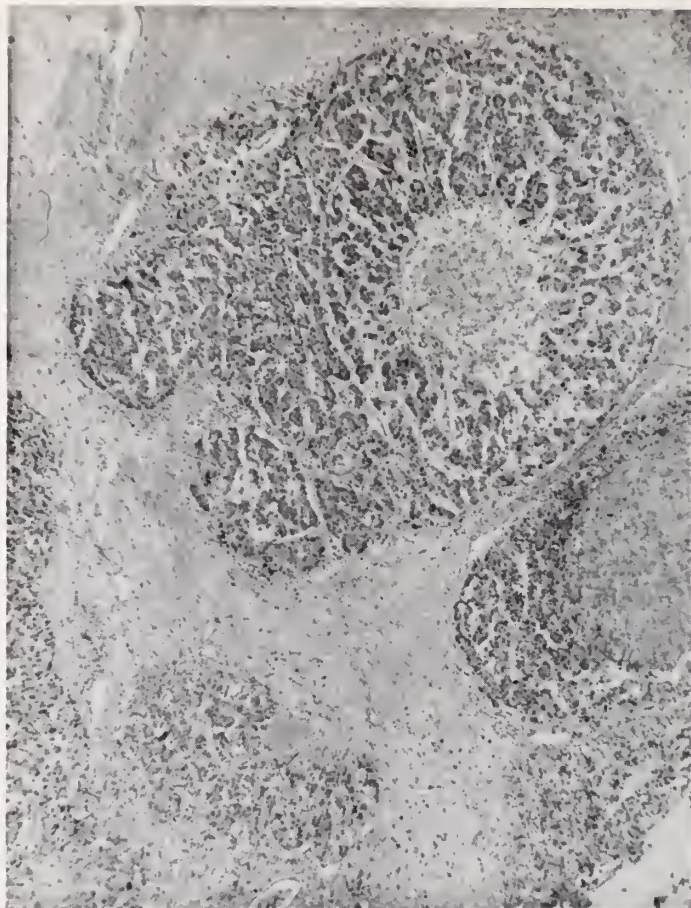


FIG. 1. Anaplastic carcinoma replacing right adrenal gland (H & E $\times 200$).

rangement and the hallmarks of primary hepatic carcinoma, namely bile production. We assume that most primary hepatic carcinomas in the alcoholic occur in the cirrhotic liver. However, this individual had virtually a normal liver. Since it is an unusual coincidence for carcinoma to develop in a non-cirrhotic liver, we looked further. When primary hepatic carcinoma develops in a cirrhotic liver, there is usually fat present and, as suspected, the normal appearing liver tissue blended into carcinomatous fatty tissue (Fig 4). In addition, there were areas of collapse in addition to carcinoma. Perhaps carcinomatous involvement of the veins led to secondary involvement of the normal parenchyma. This is conjecture, since focal cirrhotic areas were also found which appeared hamartomatous (Fig 5). I am suggesting that the hamartomatous areas were the site of carcinoma transformation. Further examination of the liver disclosed hyperplastic nodules which it was difficult to say were carcinomatous. Closer microscopic examination of the hyperplastic

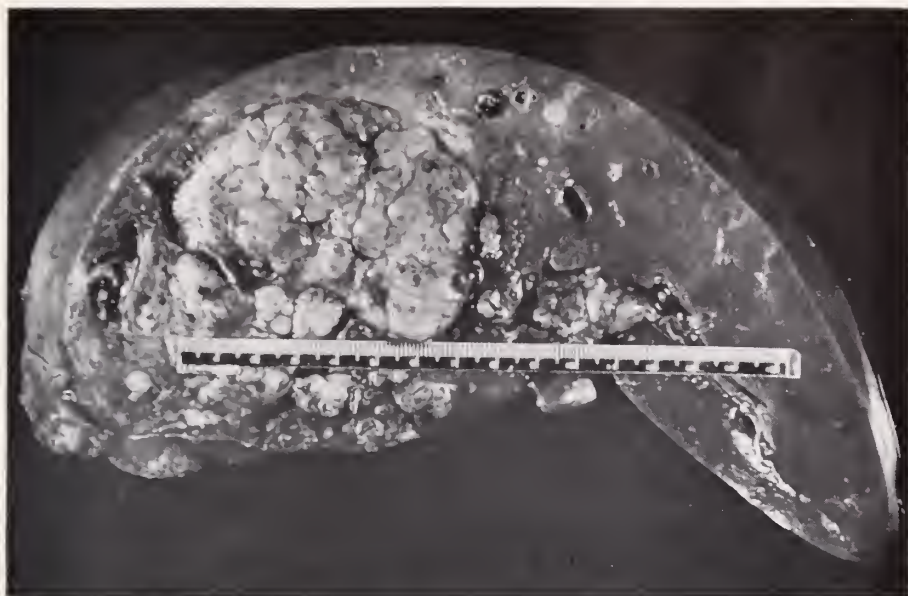


FIG. 2. Multiple tumor masses throughout liver.

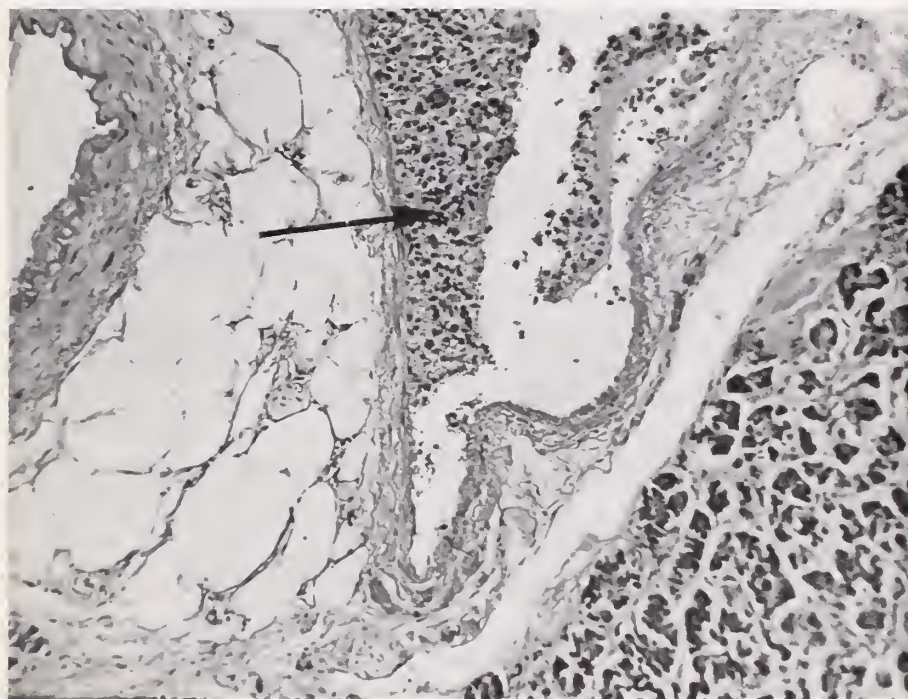


FIG. 3. Invasion of portal vein by tumor. Note tumor mass within lumen of the vessel (arrow) (H & E $\times 200$).

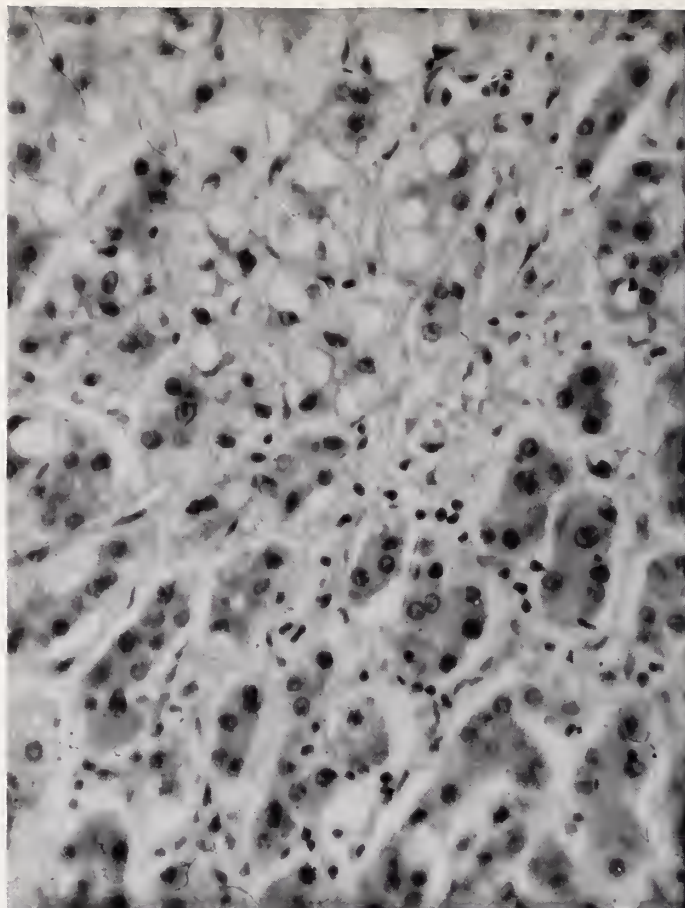


FIG. 4. Normal appearing hepatocytes blend with fatty tissue containing carcinoma (H & E $\times 600$).

nodules revealed liver cords which were arranged entirely differently from the normal parenchyma (Fig 6).

Experimental animals on carcinoma-producing diet develop hyperplastic nodules without cirrhosis or septal inflammation and this type of diffuse nodular hyperplasia of the liver can be completely overlooked in a biopsy specimen. The fibrosis and nodular hyperplasia probably were both the result of the preceding injury and may have led to focal cirrhosis, although the irregular hepatic fibrosis did not produce liver insufficiency or alterations of liver function. Alcoholic liver injury leads to two histologic alterations; one is steatosis and, if abundant, produces portal and parenchymal granulomas which may result in portal fibrosis. Alcohol also produces a hepatitis. However, histologically, there was no evidence of alcoholic hepatitis. Fauvert was probably the first to point out the paraneoplastic manifestation of carcinoma and noted that a myeloma-like blood picture may be combined

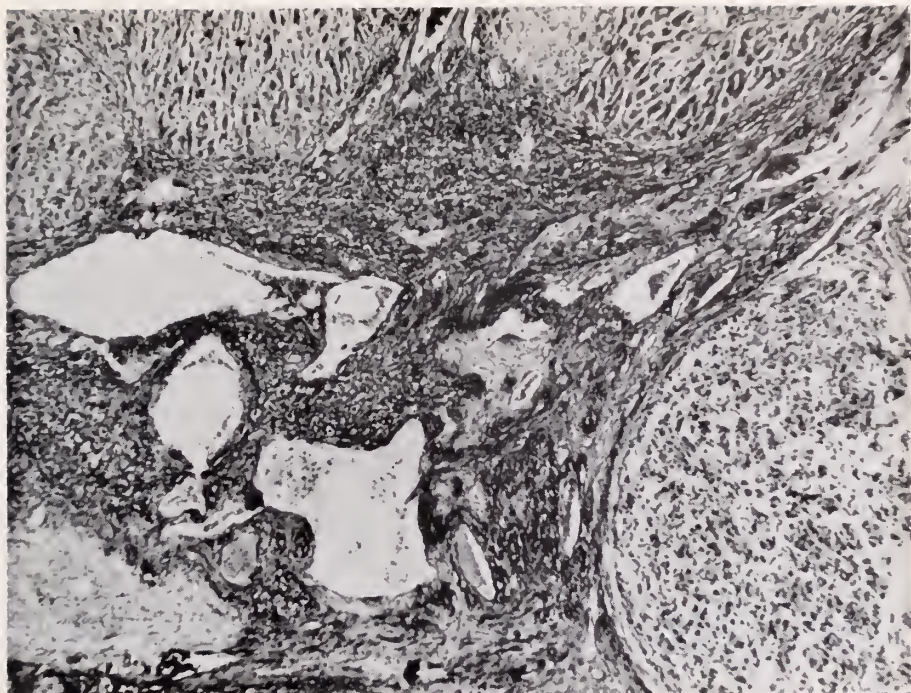


FIG. 5. Focal cirrhotic area within liver having hamartomatous appearance (H & E $\times 200$).

with high gamma globulin. Primary hepatic carcinoma also may be associated with hypercalcemia. In this case, I wonder whether the primary hepatic carcinoma did not have parathyroid-like activity. The elevated serum potassium could represent another unusual manifestation. The carcinoma invaded the portal vein and produced portal hypertension, splenomegaly, intestinal hyperemia and esophageal varices. Whether the elevated blood urea nitrogen was due to hypercalcemia or nephrosclerosis I am unable to say. Terminally, the patient developed pneumonia and shock, possibly a result of adrenal insufficiency.

In closing, this patient had alcoholic liver disease without cirrhosis and developed a primary hepatic carcinoma which was manifested by hypercalcemia.

Dr. Gutman: I'd like to discuss the point Dr. Popper raised about a possible parathyroid hormone-like substance synthesized by this tumor. Usually, hypercalcemia in the face of skeletal metastasis is due to dissolution of bone, although there are many exceptions. In reviewing our cases of hypercalcemia many years ago we encountered one or two cases of bronchogenic carcinoma with marked hypercalcemia without discernible metastasis to the liver or bones. Recently, an increased quantity of parathyroid hormone-like substance has been demonstrated in the blood of some patients with broncho-

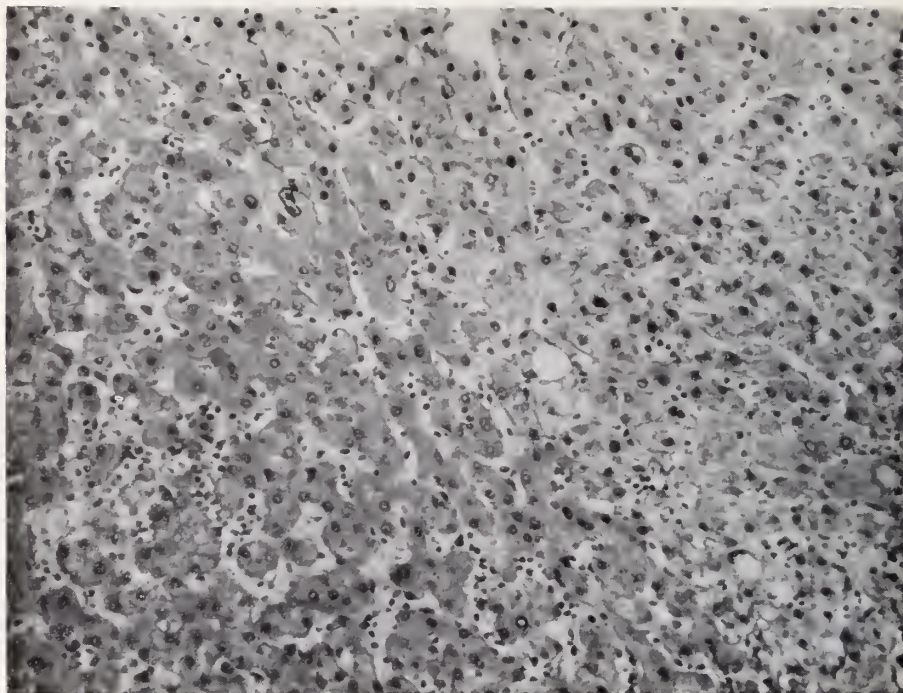


Fig. 6. Hyperplastic nodule at left containing liver cords arranged differently from normal.

genic carcinoma by Berson and others. Other tumors may be associated with overproduction of parathyroid hormone-like substances. Since, in the present case there was not extensive skeletal metastasis, we have to consider a parathyroid hormone-like effect.

The propensity to shock may have been a manifestation of adrenal insufficiency although I attributed the hypotension to the bacterial infection since it was both an early and prominent feature. The elevated serum potassium, on the other hand, I think is reasonably explained by the renal impairment. In adrenal insufficiency, sodium is exchanged for potassium and extracellular sodium enters the cells and displaces potassium. However, the serum levels of sodium were normal throughout his illness. If he had marked hyponatremia I would be more inclined to attribute the hyperkalemia to adrenal insufficiency.

The azotemia can be explained on the basis of hypercalcemia, although calcium was not found in the kidneys. However, sufficient calcium to interfere with renal function may be demonstrated by microincineration since calcium is first deposited in the renal tissues in the form of protein-bound calcium which does not stain by the usual methods.

Final diagnosis:

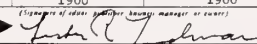
1. Primary hepatic carcinoma invading portal vein producing portal hypertension; metastasis to adrenal and lymph nodes; hypercalcemia

2. Focal cirrhosis
3. Uremic ulcerations of large and small intestines.

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courses for general practitioners

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Dermatology in General Practice.

October 2 to November 22, 1967. Monday and Thursday, 9:00 AM-10:00 AM.

Differential Diagnosis in Radiology of the Chest.

October 2 to January 29, 1968. Monday, 5:00 PM-6:00 PM.

Differential Diagnosis in Gastrointestinal Radiology.

October 3 to December 5, 1967. Tuesday, 5:00 PM-6:00 PM.

Basic Psychiatry for General Practitioners, Internists and Medical Specialists.

October 11 to June 26, 1968. Wednesday and Saturday, 9:00 AM-1:00 PM.

Psychopharmacology for Non-Psychiatrists.

October 11, 18, 25, November 1, 1967. Wednesday, 4:00 PM-5:30 PM

Clinical Hematology.

October 30 to November 1, 1967. Monday through Wednesday, 9:00 AM-5:00 PM.

Diagnosis and Treatment of Infectious Diseases—Laboratory and Clinical Aspects.

October 30 to November 10, 1967. Monday, Wednesday, Friday, 3:00 PM-5:00 PM.

Treatment of the Patient with Alcoholism Problems.

November 17, 18, 1967. Friday and Saturday, 9:00 AM-5:00 PM.

courses for specialists

Trans-meatal (Endaural) Surgery.

September 5 to 15, 1967. 9:00 AM-6:00 PM.

The Vestibular System in Otologic Diagnosis.

September 28, 29, 30, 1967. Thursday and Friday, 9:00 AM-5:00 PM. Saturday, 9:00 AM-12:00 Noon.

Group Psychotherapy for Graduate Psychiatrists.

September 11 to June 27, 1968. Monday and Thursday, 9:00 AM-12:00 Noon.

Introduction to Group Psychotherapy for Graduate Psychiatrists.

September 11 to January 29, 1968. Monday and Thursday, 9:00 AM-12:00 Noon.

Clinical Use of Radioactive Isotopes.

September 18 to May 6, 1968. Monday, 3:00 PM-6:00 PM.

Dermatopathology.

September 19 to April 23, 1968. Tuesday, 10:30 AM-12:30 PM.

Occupational Dermatology.

October 2 to December 7, 1967. Monday and Thursday, 10:00 AM-11:00 AM.

Psychiatric Complications for Obstetricians and Gynecologists.

October 21 to November 25, 1967. Saturday, 10:00 AM-12:00 Noon.

Introduction to Clinical Electroencephalography.

October 12 to December 21, 1967. Thursday, 9:00 AM-12:00 Noon.

Seminar on Legal Aspects of Psychiatry.

October 18 to May 15, 1968. Third Wednesday, 8:30 PM-10:00 PM.

Renal Biopsy as an Aid in Diagnosis and Management of Renal Disease.

November 7 to 28, 1967. Tuesday, 3:30 PM-5:00 PM.

Treatment of the Patient with Alcoholism Problems (For Graduate Psychiatrists).

November 10, 11, 1967. Friday and Saturday, 9:00 AM-5:00 PM.

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january-june, 1968

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NAME OF COURSE/DATES/HOURS

Clinical Chest Diseases. January 4 to March 7, 1968. Thursday, 4:00 PM-5:30 PM.

Laboratory Methods in Hematology.

January 29 to February 2, 1968. Monday through Friday, 9:00 AM-5:00 PM.

Dermatology in General Practice.

March 4 to 24, 1968. Monday and Thursday, 9:00 AM-11:00 AM.

Current Concepts in Obstetrics and Gynecology.

March 7 to 9, 1968. Thursday and Friday, 9:00 AM-5:00 PM, Saturday, 9:00 AM-12:00 Noon.

Laboratory Methods in Blood Banks.

March 18 to 20, 1968. Monday through Wednesday, 9:00 AM-5:00 PM.

Clinical Neurology. March 18 to 22, 1968. Monday through Friday, 9:00 AM-5:00 PM.

Differential Diagnosis in Gastrointestinal Radiology.

March 19 to May 21, 1968. Tuesday, 5:00 PM-6:00 PM.

Treatment of the Patient with Alcoholism Problems.

March 22 and 23, 1968. Friday and Saturday, 9:00 AM-5:00 PM.

Differential Diagnosis in Radiology of the Chest.

March 25 to June 10, 1968. Monday, 5:00 PM-6:00 PM.

Gastroenterology. March 25 to 29, 1968. Monday through Friday, 9:00 AM-5:00 PM.

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Clinical Electroencephalography. January 2 to May 17, 1968. Four half-days per week for 20 weeks. Hours to be arranged.

Psychopharmacology for Psychiatrists.

January 3 to February 7, 1968. Wednesday, 2:00 PM-3:30 PM.

Dermatologic Manifestations in Relation to the Other Specialties.

January 5 to February 23, 1968. Friday, 4:00 PM-5:00 PM.

Surgery of the Paranasal Sinuses.

January 29 to February 2, 1968. Monday through Friday, 8:30 AM-5:30 PM.

Introduction to Group Psychotherapy for Graduate Psychiatrists.

February 1 to June 27, 1968. Monday and Thursday, 9:00 AM-12:00 Noon.

Trans-mental (Endaural) Surgery.

February 26 to March 8, 1968. Monday through Friday, 9:00 AM-6:00 PM.

Renal Biopsy as an Aid in Diagnosis and Management of Renal Disease.

March 2 and 3, 1968. Saturday and Sunday, 9:00 AM-12:00 Noon.

Occupational Dermatology. March 4 to April 25, 1968. Monday and Thursday, 10-11 AM.

Psychodiagnostics for Psychiatrists. March 5 to April 9, 1968. Tuesday, 1:00 PM-2:30 PM.

Treatment of the Patient with Alcoholism Problems (For Graduate Psychiatrists).

March 15 and 16, 1968. Friday and Saturday, 9:00 AM-5:00 PM.

Radium Therapy.

April 30 to May 9, 1968. Tuesday, Wednesday, Thursday, 5:00 PM-7:00 PM.

Rhinoplasty and Otoplasty.

May 4 to 13, 1968, daily including Saturday and Sunday, 9:00 AM-6:00 PM.

Megavoltage Therapy.

May 13 to 24, 1968. Monday, Wednesday, and Friday, 5:00 PM-7:00 PM.

Stapes Surgery. June 3 to 14, 1968. Monday through Friday, 9:00 AM-5:00 PM.

Clinical Use of Radioactive Isotopes. June 3 to 28, 1968. Monday through Friday, 9 AM-5 PM.

INDEX TO VOLUME THIRTY-FOUR

- ABERRANT** pancreas
 duodenal ulcer in aberrant pancreas: Case report and review of literature (Ashikari et al) 2:111
- Abdominal pain and shifting masses.** (Unusual problems in surgery), 512
- ACTH** test
 effects of 9,11-Dihalogenated Corticosteroids in various types of alopecia. Part I. Clinical studies in 32 patients (Griboff et al) 2:121
- Addiction**
 mortality among young narcotic addicts (Mason) 1:4
- Adenocarcinoma** of gall bladder. (Radiological notes), 435
- Adolescence**
 mortality among young narcotic addicts (Mason) 1:4
- Alexander, D., et al.** Computer analysis of the electrocardiogram, 69
- Alonzo, M., et al.** Changing pattern of bacteremia, 601
- Alopecia**
 effects of 9,11-Dihalogenated Corticosteroids in various types of alopecia. Part I. Clinical studies in 32 patients (Griboff et al) 2:121
 pituitary-adrenal responsiveness in patients treated with 16 α -Methyl-Dichlorisone Alcohol. Part II. (Griboff et al) 2:130
- Altman, B., et al.** Emergency liver resection for primary carcinoma, 547
- Anderson, P. J., et al.** The muscle biopsy program at Mount Sinai Hospital: Results of a five year prospective study, 171
- Arthritis**
 surgery of the hand in rheumatoid arthritis (Levy) 2:103
- Ashikari, R., et al.** Duodenal ulcer in aberrant pancreas: case report and review of literature, 111
- Automation**
 computerization of serials record handling in the medical school library. (Lemkau), 595
- BACTEREMIA**, changing pattern
 changing pattern of bacteremia. (Schneerson et al), 601
- Bacterial drug resistance:** current perspectives. (R. J. Schnitzer), 489
- Barka, T., et al.** Proposed curriculum for The Mount Sinai School of Medicine, 366
- Beck, A. R., Editor.** See Unusual problems in surgery
- Benign esophageal stenosis.** (Unusual problems in surgery), 417
- Bick, E. M.** Senile arthrosis of the knee joints: degenerative osteoarthritis, 146
- Bloch, C., Editor.** See Radiological notes
- Bloch, C., et al.** Diffuse small intestinal abnormality due to *Giardia Lamblia* with roentgen and clinical reversibility after therapy: case report, 116
- Block, S. R.** A student's view, 361
- Blumenkranz, J.** What kind of architecture for education for health? 348
- Bonner, R. E., et al.** Computer analysis of the electrocardiogram, 69
- Brinberg, L.** The surfaces and planes of three-dimensional computer-drawn vectorecardiogram, 331
- Brooks, G. L.** A new independent medical college seeks the university, 237
- Burrows, L., Editor.** See Unusual problems in surgery
- CALCIFYING** hepatic metastases from colonic adenocarcinoma, (Radiological notes), 66
- Carcinoma** of the male breast. (S. Edelman), 578
- Cardiography**, computer analysis computer analysis of the electrocardiogram (Pordy et al) 1:71
- Cavernous hemangioma** of ileum, (Radiological notes), 540
- Challenges** to new medical schools. (J. R. Ellis), 260
- Changing pattern** of bacteremia. (S. S. Schneerson, C. Herschberger, and M. Alonzo), 601
- Chesky, K., et al.** Computer analysis of the electrocardiogram, 69
- Christakis, G., et al.** Proposed curriculum for The Mount Sinai School of Medicine, 366
- Clinical evaluation** of patients with neuromuscular disorders. (P. Slotwiner), 17
- Clinico-pathological conference**, F. M. Klion, Editor
 Hypercalcemia and azotemia with terminal hypotension, 50
 Liver disease in an alcoholic male, 616
 Malabsorption in an elderly male, 519
 Purpuric rash and pancytopenia in an elderly female, 161
- Community and professional problems** with a new medical school. (M. K. DuVal, Jr.), 227
- Computer analysis** of the electrocardiogram. (L. Pordy, H. Jaffee, K. Chesky, C. K. Friedberg, R. E. Bonner, H. D. Schwetman, and D. Alexander), 69
- Computer-drawn vectorecardiogram**
 the surfaces and planes of three-dimensional computer-drawn vectorecardiogram (Brinberg) 3:33
- Computerization** of serials records in the medical school library. (H. L. Lemkau), 595

- Congenital diverticulum of bladder floor. (Radiological notes), 312
- Congenital web in lower esophagus. (Radiological notes), 319
- Cooper, J. A. D., et al. An integrated program for premedical and medical education—its impact on the university, 249
- Correlation between the teaching of medicine and human biology. (R. Debré), 280
- Correlation technique
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Corticosteroids, 9,11-Dihalogenated
effects of 9,11-Dihalogenated Corticosteroids in various types of alopecia. Part I. Clinical studies in 32 patients (Griboff et al) 2:121
- Corticosteroids, 9,11-Dihalogenated, Therapeutic, Side-effects
pituitary-adrenal responsiveness in patients treated with 16 α -Methyl-Dichlorisone Alcohol. Part II. (Griboff et al) 2:130
- D**ANIEL Stats Memorial prize winner, Announcement, 90
- Data processing
computerization of serials record handling in the medical school library. (Lemkau), 595
- Davidson, C. S. Student revolt and our medical schools, 356
- Debré, R. Correlation between the teaching of medicine and human biology, 280
- Design of the university for medical and natural sciences, Ulm, Germany. (L. Heilmeyer), 285
- Diabetes
effect of probenecid on serum lipids: a study of diabetics and non-diabetics without gout (Schwartz et al) 2:96
- Diamond, S. P. Observations on some methods of clinical neurophysiology, 25
- Dichlorisone
effects of 9,11-Dihalogenated Corticosteroids in various types of alopecia. Part I. Clinical studies in 32 patients (Griboff et al) 2:121
- Diffuse small intestinal abnormality due to *Giardia Lamblia* with roentgen and clinical reversibility after therapy: Case report. (C. Bloch, and L. R. Tuchman), 116
- Dittmar, K., Daniel Stats Memorial Prize winner, Announcement, 90
- Diverticulitis of descending colon simulating carcinoma. (Radiological notes), 543
- Dreiling, D. A., et al. Duodenal ulcer in aberrant pancreas: Case report and review of literature, 111
- Duodenal ulcer in aberrant pancreas: Case report and review of literature. (R. Ashikari, M. Roberts, and D. A. Dreiling), 111
- DuVal, M. K. Jr. Community and professional problems with a new medical school, 227
- E**EDELMAN, S. Carcinoma of the male breast, 578
- Effect of Probenecid on serum lipids: A study of diabetics and non-diabetics without gout, The. (M. J. Schwartz, S. Mirsky, and W. Futterweit), 96
- Effects of 9,11-Dihalogenated Corticosteroids in various types of alopecia. Part I. Clinical studies in 32 patients. (S. I. Griboff, and W. Futterweit), 121
- Ein, S. H., et al. Ralph Colp Award winner, Announcement, 89
- Electrocardiogram, computer analysis
computer analysis of the electrocardiogram (Pordy et al) 1:71
- Electroencephalography
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Electromyography
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Electroretinography
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Ellis, J. R. Challenges to new medical schools, 260
- Elster, S. K. Obituary: Henry Horn, M.D., 1
- Emergency liver resection for primary carcinoma. (R. G. Margolese, B. Altman, and A. E. Kark), 547
- Evoked potential
observations on some methods of clinical neurophysiology (Diamond) 1:25
- F**AMILIAL polyposis. (Radiological notes), 150
- Feitelberg, S. Physics, biology and medicine, 378
- Fitz, R. H., et al. New medical education in the old southwest, 302
- Freedman, S., et al. Intussusception in acute lymphoblastic leukemia, 484
- Frequency analysis
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Friedberg, C. K., et al. Computer analysis of the electrocardiogram, 69
- Futterweit, W., et al. Effect of Probenecid on serum lipids: a study of diabetics and non-diabetics without gout, The, 96
- Futterweit, W., et al. Effects of 9,11-Dihalogenated Corticosteroids in various types of alopecia. Part I. Clinical studies in 32 patients, 121
- Futterweit, W., et al. Pituitary-Adrenal responsiveness in patients treated with 16 α -Methyl-Dichlorisone Alcohol. Part II, 130
- G**ADBOYS, H. L., et al. Proposed curriculum for The Mount Sinai School of Medicine, 366
- Gastroduodenal intussusception due to angiofibroma of gastric antrum, (Radiological notes), 535
- Gelernt, I. M., et al. Ralph Colp Award winner, Announcement, 89
- Goal, The. (H. Popper, and D. Koffler), 401

- Graduate education and medical education: a synergism. (I. L. Schwartz), 212
- Griboff, S. I., et al. Effects of 9,11-Dihalo-genated Corticosteroids in various types of alopecia. Part I. Clinical studies in 32 patients, 121
- Griboff, S. I., et al. Pituitary-Adrenal responsiveness in patients treated with 16 α -Methyl-Dichlorisone Alcohol. Part II, 130
- Gusberg, S. B. The teaching hospital experience, 91
- Grzegorzewski, E. Starting a medical school in a developing country: problems and approaches, 267

- HAIMOV, M.**, et al. Intussusception in acute lymphoblastic leukemia, 484
- Iamartoma of lung observed over a nineteen year period. (Radiological notes), 315
- Hand surgery
surgery of the hand in rheumatoid arthritis (Levy) 2:103
- Harrell, G. T. Physical facilities for the educational program, 333
- Heilmeyer, L. Design of the university for medical and natural sciences, Ulm, Germany, 285
- Heroin
mortality among young narcotic addicts (Mason) 1:4
- Herniation and strangulated incarceration of small intestines in the Foramen of Morgagni. (G. Rossi, and M. Weiss), 38
- Herschberger, C., et al. Changing pattern of bacteremia, 601
- Hospital, psychiatric unit
psychiatric aftercare: an opportunity and a challenge (Safirstein) 2:135
- Hydatid cyst of liver with abscess rupture, empyema, and broncho-hepatic-cystic fistula. (Unusual problems in surgery), 496
- Hypercalcemia and azotemia with terminal hypotension. (Clinicopathological conference), 52
- Hypernephroma
spontaneous disappearance of pulmonary metastases in hypernephroma: final report of twenty year follow-up after nephrectomy (Schapira) 1:11

- INTEGRATED** program for premedical and medical education—its impact on the university, an. (J. A. D. Cooper, and A. Lein), 249
- Intussuscepting colonic lipoma. (Radiological notes), 425
- Intussusception in acute lymphoblastic leukemia. (M. Haimov, S. Freedman, and M. T. Khilnani), 484

- JACOBSON, J. H.**, et al. Postsympathectomy neuralgia, 574
- Jaffe, H., et al. Computer analysis of the electrocardiogram, 69
- James, G. Medical education: medical technique or disease control?, 209

- KARK, A. E.**, et al. Emergency liver resection for primary carcinoma, 547
- Kaufman, M. R., The psychiatrist's dilemma, 389
- Khilnani, M. T., et al. Intussusception in acute lymphoblastic leukemia, 484
- King, D. W. Pathobiology—definition, 382
- Kirschner, P. A. Mediastinoscopy: experiences with fifty cases, 559
- Klion, F. M., Editor, See Clinico-pathological conference
- Knee joint
senile arthrosis of the knee joints: degenerative osteoarthritis (Bick) 2:146
- Koffler, D., et al. The Goal, 401
- Koffler, D., et al. Proposed curriculum for The Mount Sinai School of Medicine, 366

- LEIBOWITZ, D. A.**, et al. See Lung hernia. (Unusual problems in surgery), 507
- Leichtling, J. J., Editor, See Unusual problems in surgery
- Lein, A., et al. An integrated program for premedical and medical education—its impact on the university, 249
- Leiomyoma of ileum presenting as fever of unknown origin. (Radiological notes), 309
- Lemkau, H. L. Computerization of serials records in the medical school library, 595
- Leukemia
intussusception in acute lymphoblastic leukemia. (Khilnani et al), 484
- Levy, R. N. Surgery of the hand in rheumatoid arthritis, 103
- Libraries, automation
computerization of serials record handling in the medical school library. (Lemkau), 595
- Lipids
effect of Probenecid on serum lipids: a study of diabetics and non-diabetics without gout (Schwartz et al) 2:96
- Liver disease in an alcoholic male. (Clinicopathological conference), 616
- Lung cancer, mediastinoscopy in
mediastinoscopy: experiences with fifty cases, 559
- Lung hernia. (Unusual problems in surgery), 507
- Lymphangioma of retroperitoneum and mesentery. (Unusual problems in surgery), 45
- Lyon, L. J. The porphyrias. A clinical review, 587

- MALABSORPTION** in an elderly male. (Clinico-pathological conference), 519
- Maloney, W. F. Medical education for tomorrow, 254
- Margolese, R. G., et al. Emergency liver resection for primary carcinoma, 547
- Mason, P. Mortality among young narcotic addicts, 4
- Meconium peritonitis. (Unusual problems in surgery), 609

- Mediastinoscopy: experiences with fifty cases. (P. A. Kirschner), 559
- Medical education for tomorrow. (W. F. Maloney), 254
- Medical education: medical technique or disease control? (G. James), 209
- Medical school—community expectations, The. (C. G. Sheps), 216
- Melanosarcoma with gastric and small bowel metastases. (Radiological notes), 64
- Membrane lung: its excuse, present status, and promise, The. (E. C. Peirce II), 437
- Metastases
spontaneous disappearance of pulmonary metastases in hypernephroma: final report of twenty year follow-up after nephrectomy (Schapira) 1:11
- Mirsky, S., et al. Effect of Probenecid on serum lipids: a study of diabetics and non-diabetics without gout, The, 96
- Mortality among young narcotic addicts. (P. Mason), 4
- Mucocele of appendix. (Radiological notes), 428
- Muscle biopsy program at Mount Sinai Hospital: Results of a five year prospective study, The. (P. J. Anderson, S. K. Song, and P. Slotwiner), 171
- Myasthenia gravis and thyroid disease. (K. E. Osserman, P. Tsairis, and L. B. Weiner), 469
- NAQVI, M., et al.** See Meconium peritonitis. (Unusual problems in surgery), 609
- Neonatal bowel necrosis and peritonitis. (Unusual problems in surgery), 410
- Netter, F. H. The role of illustration in medical education and medical progress, 396
- Neuralgia
postsympathectomy neuralgia (Silverstein et al) 6: 574
- Neurophysiology, clinical
observations on some methods of clinical neurophysiology (Diamond) 1:25
- New English medical school at the University of Nottingham, A. (G. M. Wilson), 274
- New independent medical college seeks the university, A. (G. L. Brooks), 237
- New medical education in the old southwest. (R. H. Fitz, and R. S. Stone), 302
- OBSERVATIONS** on some methods of clinical neurophysiology. (S. P. Diamond), 25
- Oppenheimer, G. D., et al. Spontaneous disappearance of pulmonary metastases in hypernephroma: final report of twenty year follow-up after nephrectomy, 11
- Organization of a medical school, The. (J. Stokes III), 295
- Osserman, K. E., et al. Myasthenia gravis and thyroid disease, 469
- Osteoarthritis
senile arthrosis of the knee joints: degenerative osteoarthritis (Bick) 2:146
- Outpatient treatment, Psychiatric psychiatric aftercare: an opportunity and a challenge (Safirstein) 2:135
- PATHOBIOLOGY**—definition. (D. W. King), 382
- Peck, H., Editor, See Radiological notes
- Peirce, E. C. II. The membrane lung: its excuse, present status, and promise, 437
- Physical facilities for the educational program. (G. T. Harrell), 333
- Physics, biology and medicine. (S. Feitelberg), 378
- Physiology, sensory
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Pituitary-Adrenal responsiveness in patients treated with 16 α -Methyl-Dichlorisone Alcohol. Part II. (S. I. Griboff, and W. Futterweit), 130
- Planes, vector loops
the surfaces and planes of three-dimensional computer-drawn vector-cardiogram (Brinberg) 3:331
- Plasma ACTH test
pituitary-adrenal responsiveness in patients treated with 16 α -Methyl-Dichlorisone Alcohol. Part II. (Griboff et al) 2:130
- Popper, H., et al. The Goal, 401
- Porty, L., et al. Computer analysis of the electrocardiogram, 69
- Porphyrias. A clinical review, The. (L. J. Lyon), 587
- Postsympathectomy neuralgia. (A. Silverstein, and J. H. Jacobson), 574
- Presacrocoxygeal cyst. (Unusual problems in surgery), 606
- Primary mesenteric venous thrombosis. (Unusual problems in surgery), 40
- Probenecid
effect of probenecid on serum lipids: a study of diabetics and non-diabetics without gout (Schwartz et al) 2:96
- Proposed curriculum for The Mount Sinai School of Medicine. (T. Barka, G. Christakis, H. L. Gadboys, D. Koffler, and F. Schaffner), 366
- Psychiatric aftercare: An opportunity and a challenge. (S. L. Safirstein), 135
- Psychiatrist's dilemma, The. (M. R. Kaufman), 389
- Pulmonary
metastases in hypernephroma, See Schapira
- Purpuric rash and pancytopenia in an elderly female. (Clinico-pathological conference), 161
- RADIOLOGICAL** notes
Adenocarcinoma of gall bladder, 435
Cavernous hemangioma of ileum, 540
Calcifying hepatic metastases from colonic adenocarcinoma, 66

- Congenital diverticulum of bladder floor, 312
- Congenital web in lower esophagus, 319
- Diverticulitis of descending colon simulating carcinoma, 543
- Familial polyposis, 150
- Gastroduodenal intussusception due to angiofibroma of gastric antrum, 535
- Hamartoma of lung observed over a nineteen year period, 315
- Intussuscepting colonic lipoma, 425
- Leiomyoma of ileum presenting as fever of unknown origin, 309
- Melanosarcoma with gastric and small bowel metastases, 64
- Mucocele of appendix, 428
- Rectal villous adenoma—Ten year follow-up, 155
- Regional enteritis of duodenum and ileum, 529
- Reticulum cell sarcoma of small bowel, 433
- Reticulum cell sarcoma involving lymph nodes of small bowel mesentery, 59
- Reticulum cell sarcoma involving stomach and small bowel, 58
- Rhabdomyosarcoma with resulting aneurysm of superficial femoral artery, 160
- Thiazide-Potassium Chloride ileal stenosis, 152
- Traumatic perforation of rectosigmoid in neonate caused by digital stimulation of rectum, 327
- Traumatic perforation of rectosigmoid in neonate caused by thermometer, 323
- Ulcerating jejunal myoma, 430
- Ralph Colp award winner, Announcement, 89
- Rectal villous adenoma—Ten year follow-up. (Radiological notes), 155
- Regional enteritis of duodenum and ileum. (Radiological notes), 529
- Reticulum cell sarcoma involving lymph nodes of small bowel mesentery. (Radiological notes), 59
- Reticulum cell sarcoma involving stomach and small bowel. (Radiological notes), 58
- Reticulum cell sarcoma of small bowel. (Radiological notes), 433
- Rhabdomyosarcoma with resulting aneurysm of superficial femoral artery. (Radiological notes), 160
- Rheumatoid arthritis
surgery of the hand in rheumatoid arthritis (Levy) 2:103
- Roberts, M., et al. Duodenal ulcer in aberrant pancreas: case report and review of literature, 111
- Role of illustration in medical education and medical progress, The. (F. H. Netter), 396
- Rossi, G., et al. Herniation and strangulated incarceration of small intestines in the Foramen of Morgagni, 38
- Rudick, J., Editor, See Unusual problems in surgery
- SAFIRSTEIN, S. L. Psychiatric aftercare: an opportunity and a challenge, 135
- Schaffner, F., et al. Proposed curriculum for The Mount Sinai School of Medicine, 366
- Schapira, H. E., et al. Spontaneous disappearance of pulmonary metastases in hypernephroma: final report of twenty year follow-up after nephrectomy, 11
- Schneierman, S. S., et al. Changing pattern of bacteremia, 601
- Schnitzer, R. J. Bacterial drug resistance, 489
- Schwartz, I. L. Graduate education and medical education: a synergism, 242
- Schwartz, M. J., et al. Effect of Probenecid on serum lipids: a study of diabetics and non-diabetics without gout, The, 96
- Schwetman, H. D., et al. Computer analysis of the electrocardiogram, 69
- Senile arthrosis of the knee joints: Degenerative osteoarthritis. (E. M. Bick), 146
- Sensory physiology
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Serials, automation
computerization of serials record handling in the medical school library. (Lemkau), 595
- Sheps, C. G. The medical school—community expectations, 216
- Signal analysis
observations on some methods of clinical neurophysiology (Diamond) 1:25
- Silverstein, A., et al. Postsympathectomy neuralgia, 574
- Slotwiner, P., et al. Muscle biopsy program at Mount Sinai Hospital: Results of a five year prospective study, The, 171
- Slotwiner, P. Clinical evaluation of patients with neuromuscular disorders, 17
- Song, S. K., et al. Muscle biopsy program at Mount Sinai Hospital: Results of a five year prospective study, The, 171
- Soutter, L. The wedding of an off-campus medical school with a community of moderate size, 222
- Spilman, E. L. The Versatile Laboratory, 342
- Spontaneous disappearance of pulmonary metastases in hypernephroma: Final Report of twenty year follow-up after nephrectomy. (H. E. Schapira, and G. D. Oppenheimer), 11
- Starting a medical school in a developing country: problems and approaches. (E. Grzegorzewski), 267
- Stetten, De W. Jr. The university in medical education, 232
- Stone, R. S., et al. New medical education in the old southwest, 302
- Stokes, J. III. The organization of a medical school, 295
- Student revolt and our medical schools. (C. S. Davidson), 356
- Student's view, A. (S. R. Block), 361
- SU-4885 test
effects of 9,11-Dihalogenated Corticos-

- teroids in various types of alopecia. Part I. Clinical studies in 32 patients (Griboff et al) 2:121
- Surfaces and planes of three-dimensional computer-drawn vectorcardiogram, The. (L. Brinberg), 331
- Surgery of the hand in rheumatoid arthritis. (R. N. Levy), 103
- Sympathectomy
postsympathectomy neuralgia (Silverstein et al) 6: 574
- TEACHING** hospital experience, The. (S. B. Gusberg), 91
- Thiazide-Potassium Chloride ileal stenosis. (Radiological notes), 152
- Three-dimensional vectorcardiogram the surfaces and planes of three-dimensional computer-drawn vectorcardiogram (Brinberg) 3:331
- Transmissible multiple drug resistance bacterial drug resistance: current perspectives. (Schnitzer), 489
- Traumatic perforation of rectosigmoid in neonate caused by digital stimulation of rectum. (Radiological notes), 327
- Traumatic perforation of rectosigmoid in neonate caused by thermometer. (Radiological notes), 323
- Tsairis, P., et al. Myasthenia gravis and thyroid disease, 469
- Tuchman, L. R., et al. Diffuse small intestinal abnormality due to *Giardia Lamblia* with roentgen and clinical reversibility after therapy: case report, 116
- Tumors**
spontaneous disappearance of pulmonary metastases in hypernephroma: final report of twenty year follow-up after nephrectomy (Schapira) 1:11
- UNIVERSITY** in medical education, The. (D. W. Stetten, Jr.), 232
- Unusual problems in surgery
Abdominal pain and shifting masses, 512
Benign esophageal stenosis, 417
Hydatid cyst of liver with abscess, rupture, empyema and broncho-hepaticocystic fistula, 496
Lung hernia, 507
Lymphangioma of retroperitoneum and mesentery, 45
Meconium peritonitis, 609
Neonatal bowel necrosis and peritonitis, 410
Presacrococcygeal cyst, 606
Primary mesenteric venous thrombosis, 40
- Urinary 17-Ketosteroids**
pituitary-adrenal responsiveness in patients treated with 16 α -Methyl-Dichlorisone Alcohol. Part II. (Griboff et al) 2:130
- VECTORCARDIOGRAPHY**
the surfaces and planes of three-dimensional computer-drawn vectorcardiogram (Brinberg) 3:331
- Versatile laboratory, The. (E. L. Spilman), 342
- WATSON-Schwartz** test
the porphyrias: a clinical review. (Lyon), 587
- Wedding of an off-campus medical school with a community of moderate size. (L. Soutter), 222
- Weiner, L. B., et al. Myasthenia gravis and thyroid disease, 469
- Weiss, M., et al. Herniation and strangulated incarceration of small intestines in the Foramen of Morgagni, 38
- What kind of architecture for education for health? (J. Blumenkranz), 348
- Wilson, G. M. A new English medical school at the university of Nottingham, 274



3. ' 35

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